

Supplementary Content

| | |
|---|----|
| eAppendix 1: Literature search strategy..... | 3 |
| eAppendix 2: Full reference list of eligible studies..... | 17 |
| eAppendix 3: Reference list of studies excluded from quantitative analysis..... | 23 |
| eTable 1. Psychometric studies for instruments used for measuring patient reported outcomes in eligible randomized controlled trials..... | 24 |
| eTable 2. Baseline characteristics of eligible randomized controlled trials ($N = 90$ RCTs)..... | 26 |
| eTable 3. Risk of bias assessment of the eligible randomized controlled trials ($N = 90$ RCTs)..... | 30 |
| eTable 4. Network estimates and their certainty in evidence (GRADE) evaluating the effects of opioid and cannabis for medical use therapy in patients with chronic non-cancer pain across different outcomes..... | 34 |
| eFigure 1. Pain, random effects consistency and inconsistency model | 35 |
| eTable 5. Pain, node splitting outputs..... | 36 |
| eFigure 2. Pain, opioids versus placebo pairwise meta-analysis random effect model | 37 |
| eFigure 3. Pain, cannabis for medical use versus placebo pairwise meta-analysis random effects model | 38 |
| eFigure 4. Physical functioning, opioids versus placebo pairwise meta-analysis random effect model..... | 39 |
| eFigure 5. Physical functioning, cannabis for medical use versus placebo pairwise meta-analysis random effect model | 39 |
| eFigure 6. Emotional functioning, opioids versus placebo pairwise meta-analysis random effect model..... | 40 |
| eFigure 7. Emotional functioning, cannabis for medical use versus placebo pairwise meta-analysis random effect model | 40 |
| eFigure 8. Role functioning, opioids versus placebo pairwise meta-analysis random effect model | 41 |
| eFigure 9. Role functioning, cannabis for medical use versus placebo pairwise meta-analysis random effect model..... | 41 |
| eFigure 10. Social functioning, opioids versus placebo pairwise meta-analysis random effect model | 42 |
| eFigure 11. Social functioning, cannabis for medical use versus placebo pairwise meta-analysis random effect model | 42 |
| eFigure 12. Sleep quality, opioids versus placebo pairwise meta-analysis random effect model..... | 43 |
| eFigure 13. Sleep quality, cannabis for medical use versus placebo pairwise meta-analysis random effect model... .. | 43 |
| eFigure 14. Discontinuations due to adverse events (enriched trials), opioids versus placebo pairwise meta-analysis random effect model..... | 44 |
| eFigure 15. Discontinuations due to adverse events (enriched trials), cannabis for medical use versus placebo pairwise meta-analysis random effect model..... | 44 |
| eFigure 16. Discontinuations due to adverse events (non-enriched trials), opioids versus placebo pairwise meta-analysis random effect model..... | 45 |
| eFigure 17. Discontinuations due to adverse events (non-enriched trials), cannabis for medical use versus placebo pairwise meta-analysis random effect model | 45 |
| eAppendix 4: Reference list of cannabis for medical use studies with incomplete EQ-5D and SF-36 general health data..... | 46 |
| eTable 6. ICEMAN criteria for assessing the credibility of subgroup effects..... | 47 |
| eTable 7. Subgroup analysis for pain and secondary outcomes with moderate to high certainty evidence..... | 48 |
| eTable 8. Subgroup analysis for secondary outcomes with low certainty evidence | 49 |
| eTable 9. Network meta-regression for pain outcome, length of follow-up and sample size | 50 |
| eTable 10. Network meta-regression for secondary outcomes, length of follow-up and sample size | 50 |
| eTable 11. Network meta-analysis results for pain outcome by MME thresholds..... | 53 |
| eTable 12. Network meta-analysis results for secondary outcomes by MME thresholds..... | 53 |
| eTable 13. Pain studies from JAMA 2018 systematic review & meta-analysis included & excluded in network meta-analysis..... | 55 |
| eTable 14. Pain studies included in network meta-analysis excluded from pain JAMA 2018 systematic review & meta-analysis..... | 55 |
| eFigure 18. Funnel plot for pain for randomized trials of opioids versus placebo | 56 |
| eFigure 19. Funnel plot for pain for randomized trials of cannabis for medical use versus placebo | 56 |
| eFigure 20. Funnel plot for physical functioning for randomized trials of opioids versus placebo..... | 57 |
| eFigure 21. Funnel plot for physical functioning for randomized trials of cannabis for medical use versus placebo .. | 57 |
| eFigure 22. Funnel plot for emotional functioning for randomized trials of opioids versus placebo | 58 |
| eFigure 23. Funnel plot for emotional functioning for randomized trials of cannabis for medical use versus placebo | 59 |
| eFigure 24. Funnel plot for role functioning for randomized trials of opioids versus placebo..... | 59 |

| | |
|--|----|
| <i>eFigure 25. Funnel plot for social functioning for randomized trials of opioids versus placebo</i> | 60 |
| <i>eFigure 26. Funnel plot for sleep quality for randomized trials of opioids versus placebo.....</i> | 61 |
| <i>eFigure 27. Funnel plot for sleep quality for randomized trials of cannabis for medical use versus placebo.....</i> | 61 |

eAppendix 1: Literature search strategy

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)

Search Strategy:

- 1 (chronic adj4 pain*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (58120)
2 Chronic Pain/ (9487)
3 exp Osteoarthritis/ (54546)
4 osteoarthrit*.mp. (75997)
5 osteo-arthritis.mp. (367)
6 degenerative arthrit*.mp. (1219)
7 exp Arthritis, Rheumatoid/ (104666)
8 exp Neuralgia/ (17706)
9 Diabetic Neuropathies/ (13601)
10 (neuropath* adj5 (pain* or diabet*)).mp. (36937)
11 neuralg*.mp. (23772)
12 zoster.mp. (19225)
13 Irritable Bowel Syndrome/ (6066)
14 (IBS or irritable colon or irritable bowel).mp. (14347)
15 Migraine Disorders/ (23014)
16 migraine.mp. (34507)
17 Fibromyalgia/ (7573)
18 fibromyalg*.mp. (10324)
19 complex regional pain syndromes/ or exp causalgia/ or exp reflex sympathetic dystrophy/ (5219)
20 (complex regional pain syndromes or causalgia).mp. (2139)
21 Pain, Intractable/ (6021)
22 Phantom Limb/ (1737)
23 Hyperalgesia/ (10026)
24 ((noncancer* or non-cancer*or chronic* or recurrent or persist* or non-malign*) adj3 pain).mp. (16519)
25 or/1-24 (374187)
26 exp back pain/ or exp failed back surgery syndrome/ or exp low back pain/ (34838)
27 Radiculopathy/ or radiculopathy.mp. (8057)
28 musculoskeletal pain/ or headache/ (27891)
29 exp Arthralgia/ (10991)
30 exp Headache Disorders/ (31166)
31 headache*.mp. (83353)
32 Temporomandibular Joint Dysfunction Syndrome/ (4838)
33 ((TMJ or TMJD) and pain*).mp. (2434)
34 whiplash.mp. or exp whiplash injury/ (3756)
35 exp Cumulative Trauma Disorders/ (12612)
36 exp Peripheral Nervous System Diseases/dt [Drug Therapy] (12959)
37 Pain Measurement/de [Drug Effects] (6352)
38 (backache* or backpain* or dorsalgij* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or fibromyalgi* or myodynji* or neuralgi* or ischialgi* or crps or rachialgi*).ab,ti. (39779)
39 ((back or discogen* or bone or musculoskelet* or muscle* or skelet* or spinal or spine or vertebra* or joint* or arthritis or Intestin* or neuropath* or neck or cervical* or head or facial* or complex or radicular or cervicobrachi* or orofacial or somatic or shoulder* or knee* or hip or hips) adj3 pain).mp. (144063)
40 or/26-39 (299548)
41 (acute or emergency or preoperative or postoperative).ti,ab. (1700816)
42 40 not 41 (252546)
43 25 or 42 (532409)
44 exp Analgesics, Opioid/ (103616)
45 (opioid* or opiate*).mp. (114059)
46 (alfentanil or alphaprodine or beta-casomorphin\$ or buprenorphine or carfentanil or codeine or deltorphin or

dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or piriniramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.(143753)
47 or/44-46 (199233)
48 exp Narcotics/ (111500)
49 narcotic*.mp. (57165)
50 (adolonta or Anpec or Ardinex or Asimadoline or Alvimap or amadol or biodaligic or biokanol or Codinovo or contramal or Demerol or Dicodid or Dihydrocodeinone or dihydromorphinone or dihydrohydroxycodeinone or dihydrone or dilaudid or dinarkon or dolsin or dolosal or dolin or dolantin or dolargin or dolcontral or duramorph or duromorph or duragesic or durogesic or eucodal or Fedotzine or Fentanest or Fentora or Fortral or Hycodan or Hycon or Hydrocodone or Hydrocodeinonebitartrate or hydromorphon or hydroxycodeinon or isocodeine or isonipecain or jutadol or laudacon or l dromoran or levodroman or levorphan or levo-dromoran or levodromoran or lexir or lidol or lydol or morfin or morphine or morphia or morphin or morphinium or morphinene or morphium or ms contin or n-methylmorphine or n methylmorphine or nobligan or numorphan or oramorph or oxycodeinon or oxiconum or oxycone or oxycontin or palladone or pancodine or pethidine or phentanyl or prontofort or robidone or skenan or sublimaze or sulfentanyl or sulfentanil or sufenta or takadol or talwin or thecodin or tramadol or tramadolhameln or tramadol or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin or trasedal or theradol or tiral or topalgeic or tradol or tradolpuren or tradonal or tralgiol or tramadorsch or tramadin or tramadoc or ultram or zamudol or zumalgec or zydot or zytram).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (9563)
51 or/44-50 (227775)
52 43 and 51 (22678)
53 epidemiologic studies/ (7641)
54 exp Case-Control Studies/ (904344)
55 exp Cohort Studies/ (1723417)
56 Case control.tw. (106622)
57 (cohort adj (study or studies)).tw. (151570)
58 Cohort analy\$.tw. (6083)
59 (Follow up adj (study or studies)).tw. (44718)
60 ((observational or epidemiol*) adj (study or studies)).tw. (156420)
61 Longitudinal.tw. (201362)
62 Retrospective.mp. or prospective.tw. (1247587)
63 Cross sectional.tw. (272577)
64 Cross-sectional studies/ (260504)
65 or/53-64 (2717825)
66 exp animals/ not humans.sh. (4438182)
67 65 not 66 (2649950)
68 52 and 67 (3763)
69 randomized controlled trial.pt. (456617)
70 controlled clinical trial.pt. (92277)
71 randomized.ab. (406479)
72 placebo.ab. (187496)
73 drug therapy.fs. (2003496)
74 randomly.ab. (287373)
75 trial.ab. (422125)
76 groups.ab. (1777409)
77 or/69-76 (4167722)
78 clinical trial.mp. or clinical trial.pt. or random:mp. or tu.xs. (5199787)
79 randomized controlled trial.pt. or randomized controlled trial.mp. (476635)
80 randomized controlled trial.pt. or randomized.mp. or placebo.mp. (790362)
81 or/78-80 (5214838)
82 77 or 81 (6680171)
83 exp animals/ not humans.sh. (4438182)

84 82 not 83 (5604099)
85 43 and 51 and 84 (14496)
86 limit 85 to yr="2010 -Current" (6438)
87 68 or 86 (8377)
88 (MEDLINE or systematic review or literature search).tw. or meta analysis.mp.pt. (256038)
89 43 and 51 and 88 (881)
90 87 or 89 (8697)
91 exp Sleep Apnea Syndromes/ (30607)
92 sleep apn?ea.mp. (38637)
93 sleep-disordered breathing.mp. (5685)
94 hypogonadism.mp. or Hypogonadism/ (13040)
95 ((testosterone or androgen) and (deprivation or deficiency)).mp. (12336)
96 OPIAD.mp. (10)
97 or/91-96 (64161)
98 52 and 97 (144)
99 90 or 98 (8736)

PsycInfo**Database: PsycINFO via OVID**

Search Strategy:

1 (chronic adj4 pain*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (19944)
2 chronic pain/ (12078)
3 exp arthritis/ (3853)
4 osteoarthrit*.mp. (1758)
5 osteo-arthritis.mp. (8)
6 degenerative arthritis*.mp. (15)
7 exp neuralgia/ (892)
8 exp neuropathy/ (5931)
9 (neuropath* adj5 (pain* or diabet*)).mp. (6256)
10 neuralg*.mp. (1530)
11 zoster.mp. (550)
12 irritable bowel syndrome/ (1055)
13 (IBS or irritable colon or irritable bowel).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (1832)
14 migraine headache/ (8772)
15 migraine.mp. (11715)
16 fibromyalgia/ (1768)
17 fibromyalg*.mp. (3042)
18 complex regional pain syndromes.mp. (55)
19 "complex regional pain syndrome (type i)".mp. (137)
20 (complex regional pain syndromes or causalgia).mp. (109)
21 somatosensory disorders/ (1266)
22 hyperalgesi*.mp. (3914)
23 somatoform pain disorder/ (801)
24 somatoform disorders/ (7528)
25 conversion disorder/ (998)
26 ((noncancer* or non-cancer*or chronic* or recurrent or persist* or non-malign*) adj3 pain).mp. (3008)
27 or/1-26 (58879)
28 back pain.mp. or exp Back Pain/ (5353)
29 radiculopathy.mp. (202)
30 musculoskeletal pain.mp. (1410)
31 Arthralgia.mp. (105)
32 headache.mp. or exp HEADACHE/ (19164)
33 ((TMJ or TMJD) and pain*).mp. (142)
34 WHIPLASH/ or whiplash.mp. (571)

- 35 (backache* or backpain* or dorsalgia* or arthralgia* or polyarthralgia* or arthrodynia* or myalgia* or fibromyalgia* or myodynia* or neuralgia* or ischialgia* or crps or rachialgia*).ab,ti. (5452)
- 36 ((back or discogen* or bone or musculoskeletal* or muscle* or skeletal* or spinal or spine or vertebra* or joint* or arthritis or Intestin* or neuropath* or neck or cervical* or head or facial* or complex or radicular or cervicobrachial* or orofacial or somatic or shoulder* or knee* or hip or hips) adj3 pain).mp. (18302)
- 37 or/28-36 (39808)
- 38 (acute or emergency or preoperative or postoperative).ti,ab. (111436)
- 39 37 not 38 (35095)
- 40 27 or 39 (71492)
- 41 exp opiates/ (22978)
- 42 (opioid* or opiate*).mp. (27750)
- 43 (alfentanil or alphaprodine or beta-casomorphin\$ or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinixamide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp. (27830)
- 44 exp narcotic drugs/ (27031)
- 45 narcotic*.mp. (5729)
- 46 (adolonta or Anpec or Ardinex or Asimadoline or Alvimapam or amadol or biodalgal or biokanol or Codinovo or contramal or Demerol or Dicodid or Dihydrocodeinone or dihydromorphinone or dihydrohydroxycodeinone or dihydrone or dilaudid or dinarkon or dolsin or dolosal or dolin or dolantin or dolargin or dolcontral or duramorph or duromorph or duragesic or durogesic or eucodal or Fedotzine or Fentanest or Fentora or Fortral or Hycodan or Hycon or Hydrocodone or Hydrocodeinonebitartrate or hydromorphone or hydroxycodeinone or isocodeine or isonipecain or jutadol or laudacon or l-dromoran or levodromoran or levorphan or levo-dromoran or levodromoran or lexir or lidol or lydol or morfin or morphine or morphia or morphin or morphinium or morphinene or morphium or ms contin or n-methylmorphine or n methylmorphine or nobligan or numorphan or oramorph or oxycodeinone or oxiconum or oxycone or oxycontin or palladone or pancodine or pethidine or phentanyl or prontofort or robidone or skenan or sublimaze or sulfentanyl or sulfentanil or sufenta or takadol or talwin or thecodin or tramadol or tramadolhameln or tramadol or tramadolor or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin or trasadal or theradol or tiral or topalgeic or tradol or tradolpure or tradonal or tralgiol or tramadorsch or tramadin or tramadoc or ultram or zamudol or zumalgec or zydot or zytram).mp. (928)
- 47 or/41-46 (47945)
- 48 37 and 47 (2028)
- 49 animals/ not humans/ (7067)
- 50 animal models/ (29760)
- 51 animal research/ (368)
- 52 exp rodents/ (201732)
- 53 (rat or rats or mouse or mice).ti. (110418)
- 54 or/49-53 (226624)
- 55 48 not 54 (1547)

Database: AMED (Allied and Complementary Medicine) via OVID

Search Strategy:

-
- 1 analgesics opioid/ (335)
- 2 (opioid* or opiate*).mp. (1449)
- 3 (alfentanil or alphaprodine or beta-casomorphin\$ or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinixamide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp. [mp=abstract, heading words, title] (1097)
- 4 narcotics/ (177)
- 5 narcotic*.mp. (345)
- 6 (adolonta or Anpec or Ardinex or Asimadoline or Alvimapam or amadol or biodalgal or biokanol or Codinovo

or contramal or Demerol or Dicodid or Dihydrocodeinone or dihydromorphinone or dihydrohydroxycodeinone or dihydrone or dilaudid or dinarkon or dolsin or dolosal or dolin or dolantin or dolargan or dolcontral or duramorph or duromorph or duragesic or durogesic or eucodal or Fedotzine or Fentanest or Fentora or Fortral or Hycodan or Hycon or Hydrocodone or Hydrocodeinonebitartrate or hydromorphon or hydroxycodeinon or isocodeine or isonipecain or jutadol or laudacon or l dromoran or levodroman or levorphan or levo-dromoran or levodromoran or lexir or lidol or lydol or morfin or morphine or morphin or morphinium or morphinene or morphium or ms contin or n-methylmorphine or n methylmorphine or nobigan or numorphan or oramorph or oxycodeinon or oxiconum or oxycone or oxycontin or palladone or pancodine or pethidine or phentanyl or prontofort or robidone or skenan or sublimaze or sulfentanyl or sulfentanil or sufenta or takadol or talwin or theocodin or tramadol or tramadolhameln or tramadol or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin or trasadal or theradol or tiral or topalgeic or tradol or tradolpuren or tradonal or tralgiol or tramadorsch or tramadin or tramadoc or ultram or zamudol or zumalgeic or zydot or zytram).mp. [mp=abstract, heading words, title] (109)
7 or/1-6 (2268)
8 (chronic adj4 pain).mp. [mp=abstract, heading words, title] (4640)
9 exp arthritis/ (5636)
10 arthralgia/ (189)
11 fibromyalgia/ (1656)
12 neuralgia/ (157)
13 diabetic neuropathies/ (264)
14 (neuropath* adj5 (pain* or diabet*)).mp. (981)
15 neuralg*.mp. [mp=abstract, heading words, title] (335)
16 osteoarthritis*.mp. [mp=abstract, heading words, title] (3321)
17 irritable bowel syndrome/ (133)
18 (IBS or irritable colon or irritable bowel).mp. [mp=abstract, heading words, title] (297)
19 fibromyalg*.mp. [mp=abstract, heading words, title] (1846)
20 Migraine/ or migraine.mp. (651)
21 complex regional pain syndromes/ or reflex sympathetic dystrophy/ (188)
22 (complex regional pain syndromes or causalgia).mp. [mp=abstract, heading words, title] (77)
23 pain intractable/ (431)
24 hyperalgesia/ or phantom limb/ (181)
25 ((noncancer* or non-cancer* or chronic* or recurrent or persist* or non-malign*) adj3 pain).mp. [mp=abstract, heading words, title] (675)
26 or/8-25 (15230)
27 exp backache/ (6186)
28 radiculopathy.mp. (290)
29 exp Headache/ or headache.mp. (1709)
30 Temporomandibular joint syndrome/ (67)
31 ((TMJ or TMJD) and pain*).mp. (28)
32 Whiplash injuries/ or whiplash.mp. (594)
33 repetition strain injury/ (312)
34 (backache* or backpain* or dorsalgia* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or fibromyalgi* or myodyn* or neuralgi* or ischialgi* or crps or rachialgi*).ab,ti. (2429)
35 ((back or discogen* or bone or musculoskelet* or muscle* or skelet* or spinal or spine or vertebra* or joint* or arthritis or Intestin* or neuropath* or neck or cervical* or head or facial* or complex or radicular or cervicobrachi* or orofacial or somatic or shoulder* or knee* or hip or hips) adj3 pain).mp. (12871)
36 or/27-35 (17684)
37 (acute or emergency or preoperative or postoperative).ti,ab. (12782)
38 36 not 37 (16319)
39 26 or 38 (25280)
40 7 and 39 (532)
41 (rat or rats or mouse or mice).ti. (5925)
42 animals/ not humans/ (7083)
43 exp Rodents/ (8142)
44 41 or 42 or 43 (10161)
45 40 not 44 (512)

Central (Cochrane Library via Wiley)

Description:**ID Search Hits**

- #1 chronic near/3 pain 9973
- #2 MeSH descriptor: [Chronic Pain] explode all trees 1178
- #3 MeSH descriptor: [Osteoarthritis] explode all trees 4754
- #4 osteoarthrit* 10561
- #5 osteo-arthritis 69
- #6 degenerative arthrit* 359
- #7 MeSH descriptor: [Arthritis, Rheumatoid] explode all trees 4858
- #8 MeSH descriptor: [Neuralgia] explode all trees 1049
- #9 MeSH descriptor: [Diabetic Neuropathies] explode all trees 1397
- #10 neuropath* near/5 (pain* or diabet*) 4465
- #11 neuralg* 1913
- #12 zoster 1641
- #13 MeSH descriptor: [Irritable Bowel Syndrome] explode all trees 674
- #14 irritable (colon or bowel) 2448
- #15 IBS 1629
- #16 MeSH descriptor: [Migraine Disorders] explode all trees 1959
- #17 migraine 4659
- #18 MeSH descriptor: [Fibromyalgia] explode all trees 851
- #19 fibromyalg* 1987
- #20 MeSH descriptor: [Complex Regional Pain Syndromes] explode all trees 238
- #21 complex regional pain syndromes or causalgia 203
- #22 MeSH descriptor: [Pain, Intractable] explode all trees 273
- #23 MeSH descriptor: [Phantom Limb] explode all trees 75
- #24 MeSH descriptor: [Hyperalgesia] explode all trees 454
- #25 ((noncancer* or non-cancer* or chronic* or recurrent or persist* or non-malign*) near/3 pain) 2107
- #26 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 40797
- #27 MeSH descriptor: [Back Pain] explode all trees 3879
- #28 MeSH descriptor: [Radiculopathy] explode all trees 303
- #29 MeSH descriptor: [Musculoskeletal Pain] explode all trees 478
- #30 MeSH descriptor: [Arthralgia] explode all trees 1313
- #31 MeSH descriptor: [Headache Disorders] explode all trees 2415
- #32 MeSH descriptor: [Headache] explode all trees 1798
- #33 headache* 26942
- #34 MeSH descriptor: [Temporomandibular Joint Dysfunction Syndrome] explode all trees 179
- #35 ((TMJ or TMJD) and pain*) 266
- #36 MeSH descriptor: [Whiplash Injuries] explode all trees 208
- #37 whiplash 460
- #38 MeSH descriptor: [Cumulative Trauma Disorders] explode all trees 668
- #39 backache* or backpain* or dorsalmg* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or fibromyalgi* or myodyn* or neuralg* or ischialg* or crps or rachialg* 13481
- #40 ((back or discogen* or bone or musculoskelet* or muscle* or skelet* or spinal or spine or vertebra* or joint* or arthritis or Intestin* or neuropath* or neck or cervical* or head or facial* or complex or radicular or cervicobrachi* or orofacial or somatic or shoulder* or knee* or hip or hips) near/3 pain) 28955
- #41 radiculopathy 893
- #42 #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 60275
- #43 acute or emergency or preoperative or postoperative 200646
- #44 42 not 43 59058
- #45 #26 or #44 97623
- #46 opioid* or opiate* 17932
- #47 narcotic* 6752
- #48 MeSH descriptor: [Analgesics, Opioid] explode all trees 6462
- #49 MeSH descriptor: [Narcotics] explode all trees 7246

#50 alfentanil or alphaprodine or beta-casomorphin\$ or buprenorphine or carfentanil or codeine or deltorphan or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirnitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol 32420
#51adolonta or Anpec or Ardinex or Asimadoline or Alvimopam or amadol or biodaligic or biokanol or Codinovo or contramal or Demerol or Dicodid or Dihydrocodeinone or dihydromorphinone or dihydrohydroxycodeinone or dihydrone or dilaudid or dinarkon or dolsin or dolosal or dolin or dolantin or dolargin or dolcontral or duramorph or duromorph or duragesic or durogesic or eucodal or Fedotzine or Fentanest or Fentora or Fortral or Hycodan or Hycon or Hydrocodone or Hydrocodeinonebitartrate or hydromorphon or hydroxycodeinon or isocodeine or isonipecain or jutadol or laudacon or l dromoran or levodroman or levorphan or levo-dromoran or levodromoran or lexit or lidol or lydol or morfin or morfine or morphia or morphin or morphinium or morphinene or morphium or ms contin or n-methylmorphine or n methylmorphine or nobligan or numorphan or oramorph or oxycodeinon or oxiconum or oxycone or oxycontin or palladone or pancodine or pethidine or phentanyl or prontofort or robidone or skenan or sublimaze or sulfentanyl or sulfentanil or sufenta or takadol or talwin or thecodin or tramadol or tramadolhameln or tramadol or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin or trasedal or theradol or tiral or topalgic or tradol or tradolpuren or tradonal or tralgiol or tramadorsch or tramadin or tramadol or ultram or zamuadol or zumalgc or zydot or zytram 5622
#52 #46 or #47 or #48 or #49 or #50 or #51 42294
#53 #45 and #52 2656

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)

Search Strategy:

- 1 Cannabis/ (11443)
2 exp cannabinoids/ or cannabidiol/ or cannabinol/ or dronabinol/ (16399)
3 Endocannabinoids/ (6489)
4 exp Receptors, Cannabinoid/ (10396)
5 (Cannabis or cannabinol or cannabinoid* or cannabidiol or bhang or cannador or charas or ganja or ganjah or hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic acid or cannabichromene or cannabiolsoin or cannabigerol or tetrahydrocannabinol or dronabinol or levonantradol or nabiximols or palmidrol or tetrahydrocannabinolic acid or tetrahydro cannabinol or marinol or tetrabeninex or sativex or endocannabinoid*).mp. (64927)
6 or/1-5 (64927)
7 pain*.mp.jw. or Pain/ (890667)
8 exp Osteoarthritis/ or exp Arthritis, Rheumatoid/ or exp Neuralgia/ or Diabetic Neuropathies/ or Irritable Bowel Syndrome/ or Migraine Disorders/ or Fibromyalgia/ or complex regional pain syndromes/ or exp causalgia/ or exp reflex sympathetic dystrophy/ or Pain, Intractable/ or chronic pain/ or Phantom Limb/ or Hyperalgesia/ or exp back pain/ or exp failed back surgery syndrome/ or exp low back pain/ or Radiculopathy/ or musculoskeletal pain/ or headache/ or exp Arthralgia/ or exp Headache Disorders/ or Temporomandibular Joint Dysfunction Syndrome/ or exp whiplash injury/ or exp Cumulative Trauma Disorders/ or exp Peripheral Nervous System Diseases/dt or Pain Measurement/de (423216)
9 ((irrita* or inflam*) adj4 (bowel or colon)).mp. (81237)
10 (osteoarthrit* or osteo-arthritis or arthrit* or neuropath* or neuralgi* or zoster* or migraine* or headache* or fibromyalgi* or causalgia or radiculopathy* or whiplash or backache* or backpain* or dorsalg* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or myodyn* or ischialgi* or crps or rachialgi* or TMJ or TMJD or IBS or crohn* or colitis* or enteritis* or ileitis*).mp. (827784)
11 Muscle Spasticity/ (9871)
12 Muscle Hypertonia/ (1033)
13 (spasticity or spasm or spastic or hypertonia).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (56343)
14 or/7-13 (1660232)

- 15 6 and 14 (6752)
16 random:.tw. or placebo:.mp. or double-blind:.tw. (1409704)
17 ((treatment or control) adj3 group*).ab. (680082)
18 (allocat* adj5 group*).ab. (29935)
19 ((clinical or control*) adj3 trial).ti,ab,kw. (333663)
20 or/16-19 (1961120)
21 randomized controlled trial.pt. (561669)
22 controlled clinical trial.pt. (94744)
23 clinical trials as topic.sh. (199529)
24 randomly.ab. (378041)
25 trial.ti. (258476)
26 drug therapy.fs. (2458509)
27 or/16-26 (4232754)
28 15 and 27 (3200)
29 animals/ not humans/ (4940789)
30 28 not 29 (2513)

EMBASE (OVID)

Search Strategy:

- 1 cannabis/ (39161)
2 exp cannabinoid/ (76903)
3 medical cannabis/ (3242)
4 exp cannabinoid receptor/ (16300)
5 exp endocannabinoid/ (10122)
6 (Cannabis or cannabinol or cannabinoid* or cannabidiol or bhang or cannador or charas or ganja or ganjah or hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic acid or cannabichromene or cannabiolsoin or cannabigerol or tetrahydrocannabinol or dronabinol or levonantradol or nabiximols or palmidrol or tetrahydrocannabinolic acid or tetrahydro cannabinol or marinol or tetrabenex or sativex or endocannabinoid*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (101727)
7 or/1-6 (103167)
8 pain/ or pain*.mp. (1523452)
9 chronic pain/ or exp osteoarthritis/ or exp rheumatoid arthritis/ or exp neuralgia/ or diabetic neuropathy/ or irritable colon/ or exp migraine/ or fibromyalgia/ or intractable pain/ or agnosia/ or exp radiculopathy/ or musculoskeletal pain/ or exp arthralgia/ or headache/ or temporomandibular joint disorder/ or whiplash injury/ or exp cumulative trauma disorder/ (947642)
10 (osteoarthritis* or osteo-arthritis or arthritis* or neuropath* or neuralgi* or zoster* or migraine* or headache* or fibromyalgi* or causalgia or radiculopathy* or whiplash or backache* or backpain* or dorsalgji* or arthralgi* or polyarthralgi* or arthrodynji* or myalgi* or myodynji* or ischialgji* or crps or rachialgji*or TMJ or TMJD or IBS or crohn* or colitis* or enteritis* or ileitis*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (1588678)
11 ((irrita* or inflam*) adj4 (bowel or colon)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (143101)
12 muscle hypertonia/ or spasticity/ (29975)
13 (spasticity or spasm or spastic or hypertonia).mp. (102572)
14 or/8-13 (2856349)
15 7 and 14 (15652)
16 clinical article/ (2840832)
17 exp clinical study/ (11038373)
18 clinical trial/ (1030530)
19 controlled study/ (8707614)
20 randomized controlled trial/ (700351)

21 major clinical study/ (4407914)
22 double blind procedure/ (193251)
23 multicenter study/ (318443)
24 single blind procedure/ (45524)
25 phase 3 clinical trial/ (59538)
26 phase 4 clinical trial/ (4691)
27 crossover procedure/ (69709)
28 placebo/ (378215)
29 or/16-28 (15939371)
30 allocat\$.mp. (195320)
31 assign\$.mp. (446472)
32 blind\$.mp. (548005)
33 (clinic\$.adj25 (study or trial)).mp. (7617865)
34 compar\$.mp. (9098845)
35 control\$.mp. (12329430)
36 cross?over.mp. (108597)
37 factorial\$.mp. (69675)
38 follow?up.mp. (50719)
39 placebo\$.mp. (491115)
40 prospectiv\$.mp. (1372469)
41 random\$.mp. (2010437)
42 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).mp. (348231)
43 trial.mp. (2377246)
44 (versus or vs).mp. (2518554)
45 or/30-44 (19623398)
46 29 and 45 (12865583)
47 exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/ (30266244)
48 human/ or normal human/ or human cell/ (23473918)
49 47 and 48 (23405621)
50 47 not 49 (6860623)
51 46 not 50 (10162086)
52 randomized controlled trial.pt. or randomi?ed.mp. or placebo.mp. (1559060)
53 ((treatment or control) adj3 group*).ab. (985064)
54 (allocat* adj5 group*).ab. (39102)
55 ((clinical or control*) adj3 trial).ti,ab,kw. (472392)
56 52 or 53 or 54 or 55 (2453456)
57 15 and 51 (5650)
58 15 and 56 (2581)
59 57 or 58 (6324)

AMED (OVID)**Database: AMED (Allied and Complementary Medicine)**

Search Strategy:

1 exp cannabis/ (250)
2 cannabinoids/ (59)
3 (Cannabis or cannabinol or cannabinoid* or cannabidiol or bhang or cannador or charas or ganja or ganjah or hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic acid or cannabichromene or cannabiolsoin or cannabigerol or tetrahydrocannabinol or dronabinol or levonantradol or nabiximols or palmidrol or tetrahydrocannabinolic acid or tetrahydro cannabinol or marinol or tetrabenex or sativex or endocannabinoid*).mp. [mp=abstract, heading words, title] (434)
4 or/1-3 (434)
5 pain.mp. or Pain/ (35918)
6 exp arthritis rheumatoid/ or exp osteoarthritis/ (5358)
7 exp pain/ or neuralgia/ (23893)

- 8 exp diabetic neuropathies/ (1040)
- 9 irritable bowel syndrome/ (199)
- 10 Migraine/ (513)
- 11 fibromyalgia/ or myofascial pain syndromes/ or temporomandibular joint syndrome/ (2280)
- 12 complex regional pain syndromes/ or reflex sympathetic dystrophy/ (197)
- 13 Phantom limb/ (134)
- 14 hyperalgesia/ (74)
- 15 whiplash injuries/ (546)
- 16 repetition strain injury/ (324)
- 17 (osteoarthritis* or osteo-arthritis or arthrit* or neuropath* or neuralgi* or zoster* or migraine* or headache* or fibromyalgi* or causalgia or radiculopathy* or whiplash or backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or myodyn* or ischialgi* or crps or rachialgi* or TMJ or TMJD or IBS or crohn* or colitis* or enteritis* or ileitis*).mp. (18652)
- 18 ((irrita* or inflam*) adj4 (bowel or colon)).mp. (585)
- 19 Muscle spasticity/ (1183)
- 20 Muscle hypertonia/ (84)
- 21 (spasticity or spasm or spastic or hypertonia).mp. [mp=abstract, heading words, title] (2678)
- 22 or/5-21 (50501)
- 23 4 and 22 (118)

PsycInfo (OVID)**Database: APA PsycInfo**

Search Strategy:

- 1 exp cannabis/ or exp cannabinoids/ or tetrahydrocannabinol/ (15070)
- 2 (Cannabis or cannabinol or cannabinoid* or cannabidiol or bhang or cannador or charas or ganja or ganjah or hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic acid or cannabichromene or cannabiolsoin or cannabigerol or tetrahydrocannabinol or dronabinol or levonantradol or nabiximols or palmidrol or tetrahydrocannabinolic acid or tetrahydro cannabinol or marinol or tetrabinex or sativex or endocannabinoid*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] (30531)
- 3 1 or 2 (30531)
- 4 pain*.mp. or exp PAIN/ (140896)
- 5 (osteoarthritis* or osteo-arthritis or arthrit* or neuropath* or neuralgi* or zoster* or migraine* or headache* or fibromyalgi* or causalgia or radiculopathy* or whiplash or backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or myodyn* or ischialgi* or crps or rachialgi* or TMJ or TMJD or IBS or crohn* or colitis* or enteritis* or ileitis*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] (74571)
- 6 4 or 5 (180976)
- 7 3 and 6 (2094)
- 8 limit 7 to "therapy (best balance of sensitivity and specificity)" (372)
- 9 (double-blind or random: assigned or control).tw. (522132)
- 10 clinical trials/ (12034)
- 11 (controlled adj3 trial*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] (58491)
- 12 (clinical adj2 trial*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] (50934)
- 13 (randomi?ed adj7 trial*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] (69435)
- 14 or/9-13 (589510)
- 15 7 and 14 (525)
- 16 8 or 15 (525)
- 17 muscle spasms/ (522)
- 18 (spasticity or spasm or spastic or hypertonia).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] (5660)

- 19 17 or 18 (5767)
 20 3 and 19 (129)
 21 limit 20 to "therapy (best balance of sensitivity and specificity)" (36)
 22 14 and 20 (80)
 23 21 or 22 (80)
 24 16 or 23 (548)

Cochrane Library (Wiley)

| ID | Search | Hits |
|-----|---|--------|
| #1 | MeSH descriptor: [Cannabis] 1 tree(s) exploded | 10 |
| #2 | MeSH descriptor: [Cannabinoids] explode all trees | 928 |
| #3 | MeSH descriptor: [Endocannabinoids] explode all trees | 63 |
| #4 | MeSH descriptor: [Endocannabinoids] explode all trees | 63 |
| #5 | (Cannabis or cannabinol or cannabinoid* or cannabidiol or bhang or cannador or charas or ganja or ganjah or hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic acid or cannabichromene or cannabiolsoin or cannabigerol or tetrahydrocannabinol or dronabinol or levonantradol or nabiximols or palmidrol or tetrahydrocannabinolic acid or tetrahydro cannabinol or marinol or tetrabeninex or sativex or endocannabinoid*):ti,ab,kw (Word variations have been searched) | 5386 |
| #6 | #1 or #2 or #3 or #4 or #5 | 5386 |
| #7 | MeSH descriptor: [Pain] explode all trees | 54054 |
| #8 | (pain*):ti,ab,kw (Word variations have been searched) | 207177 |
| #9 | #7 or #8 213544 | |
| #10 | #6 and #9 | 794 |
| #11 | [mh Osteoarthritis] or [mh ^"Arthritis, Rheumatoid"] or [mh Neuralgia] or [mh ^"Diabetic Neuropathies"] or [mh ^"Irritable Bowel Syndrome"] or [mh ^"Migraine Disorders"] or [mh Fibromyalgia] or [mh ^"complex regional pain syndromes"] or [mh causalgia] or [mh ^"reflex sympathetic dystrophy"] or [mh ^"pain Intractable"] or [mh ^"Phantom Limb"] or [mh Hyperalgesia] or [mh ^"back pain"] or [mh ^"failed back surgery syndrome"] or [mh ^"low back pain"] or [mh Radiculopathy] or [mh ^"musculoskeletal pain"] or [mh headache] or [mh Arthralgia] or [mh ^"Headache Disorders"] or [mh ^"Temporomandibular Joint Dysfunction Syndrome"] or [mh ^"whiplash injury"] or [mh ^"Cumulative Trauma Disorders"] or [mh "Peripheral Nervous System Diseases"/DT] or [mh ^"Pain Measurement"/DE] | 35211 |
| #12 | (osteoarthritis* or osteo-arthritis or arthrit* or neuropath* or neuralgi* or zoster* or migraine* or headache* or fibromyalgi* or causalgia or radiculopathy* or whiplash or backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or myodyn* or ischialgi* or crps or rachialgi* or TMJ or TMJD or IBS or crohn* or colitis* or enteritis* or ileitis*) | 126119 |
| #13 | (irrita* or inflam*) near/4 (bowel or colon) | 8688 |
| #14 | #11 or #12 or #13136956 | |
| #15 | #6 and #14 | 513 |
| #16 | #10 or #15 in Trials | 909 |
| #17 | MeSH descriptor: [Muscle Spasticity] explode all trees | 999 |
| #18 | MeSH descriptor: [Muscle Hypertonia] explode all trees | 1118 |
| #19 | spasticity or spasm or spastic or hypertonia | 8777 |
| #20 | #17 or #18 or #198841 | |
| #21 | #20 and #6 | 198 |
| #22 | #10 or #15 or #21 in Trials | 1001 |

CINAHL (EBSCO)

| # | Query | Results |
|-----|---|---------|
| S51 | S49 OR S50 | 849 |
| S50 | S48 | 427 |
| S49 | S29 AND S48 | 721 |
| S48 | S4 AND S47 | 2,847 |
| S47 | S7 OR S36 OR S46 | 580,420 |
| S46 | S43 OR S44 OR S45 | 14,915 |
| S45 | TX spasticity or spasm or spastic or hypertonia | 14,915 |
| S44 | (MH "Muscle Hypertonia") | 517 |
| S43 | (MH "Muscle Spasticity") | 4,382 |
| S42 | S31 OR S41 | 802 |
| S41 | S39 OR S40 | 169 |
| S40 | S29 AND S38 | 154 |
| S39 | S38 | 49 |
| S38 | S37 NOT S8 | 464 |
| S37 | S4 AND S36 | 2,025 |
| S36 | S32 OR S33 OR S34 OR S35 | 458,156 |
| S35 | (irrita* or inflam*) N4 (bowel or colon) | 18,662 |
| S34 | TX (osteoarthrit* or osteo-arthritis or arthrit* or neuropath* or neuralgi* or zoster* or migraine* or headache* or fibromyalgi* or causalgia or radiculopathy* or whiplash or backache* or backpain* or dorsalgi* or arthalgi* or polyarthralgi* or arthrodyni* or myalgi* or myodyn* or ischialgi* or crps or rachialgi* or TMJ or TMJD or IBS or crohn* or colitis* or enteritis* or ileitis*) | 269,583 |
| S33 | (MH Pain+) OR (MH Phantom Limb) OR (MH Hyperalgesia) OR (MH back pain+) OR (MH "failed back surgery syndrome+") OR (MH "low back pain+") OR (MH Radiculopathy) OR (MH "musculoskeletal pain") OR (MH headache) OR (MH Arthralgia+) OR (MH "Headache Disorders+") OR (MH "Temporomandibular Joint Dysfunction Syndrome") OR (MH "whiplash injury+/" or (MH "Cumulative Trauma Disorders+")) | 226,279 |
| S32 | TX (MH Osteoarthritis+) OR (MH "Arthritis, Rheumatoid+") OR (MH Neuralgia) OR (MH Diabetic Neuropathies) OR (MH "Irritable Bowel Syndrome") OR (MH "Migraine Disorders" OR (MH Fibromyalgia) OR (MH "complex regional pain syndromes") OR (MH causalgia+) OR (MH "reflex sympathetic dystrophy+")) | 85,767 |
| S31 | S9 OR S30 | 633 |

| | | |
|-----|---|-----------|
| S30 | S8 AND S29 | 526 |
| S29 | S16 OR S21 OR S28 | 1,384,715 |
| S28 | S22 OR S23 OR S24 OR S25 OR S26 OR S27 | 1,181,925 |
| S27 | (MH "Prospective Studies+") | 495,834 |
| S26 | (MH "Evaluation Research+") | 330,364 |
| S25 | (MH "Comparative Studies") | 426,809 |
| S24 | "latin square" | 248 |
| S23 | (MH "Study Design") OR (MH "Crossover Design") OR (MH "Experimental Studies+") | 423,651 |
| S22 | (MH "Random Sample+") | 116,667 |
| S21 | S17 OR S18 OR S19 OR S20 | 493,219 |
| S20 | "random*" | 475,828 |
| S19 | "placebo*" | 73,590 |
| S18 | (MH "Placebos") | 13,285 |
| S17 | (MH "Placebo Effect") | 2,426 |
| S16 | S10 OR S11 OR S12 OR S13 OR S14 OR S15 | 455,728 |
| S15 | "triple-blind" | 489 |
| S14 | "single-blind" | 17,122 |
| S13 | "double-blind" | 63,811 |
| S12 | clinical W3 trial | 278,173 |
| S11 | "randomi?ed controlled trial**" | 200,563 |
| S10 | (MH "Clinical Trials+") | 333,661 |
| S9 | S4 AND S7 | 344 |
| S8 | S4 AND S7 | 2,279 |
| S7 | S5 OR S6 | 364,720 |
| S6 | "pain" | 342,481 |
| S5 | (MH "Pain+") | 223,572 |
| S4 | S1 OR S2 OR S3 | 24,367 |
| S3 | Cannabis or cannabinol or cannabinoid* or cannabidiol or bhang or cannador or charas or ganja or ganjah or hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic acid or cannabichromene or cannabielsin or cannabigerol or tetrahydrocannabinol or dronabinol or levonantradol or nabiximols or palmidrol or | 24,367 |

| | | |
|----|--|--------|
| | tetrahydrocannabinolic acid or tetrahydro cannabinol or marinol or tetranabinex or sativex or endocannabinoid* | |
| S2 | (MH "Medical Marijuana") | 2,127 |
| S1 | (MH "Cannabis") | 10,569 |

PubMed

Search: (((((((((pain* OR spasticity OR spasm OR spastic OR hypertonia OR osteoarthrit* OR osteo-arthritis OR arthrit* OR neuropath* OR neuralgi* OR zoster* OR migraine* OR headache* OR fibromyalgi* OR causalgia OR radiculopathy* OR whiplash OR backache* OR backpain* OR dorsalgi* OR arthralgi* OR polyarthralgi* OR arthrodyni* OR myalgi* OR myodyn* OR ischialgi* OR crps OR brachialgia *or tmj OR tmjd OR IBS OR crohn* OR colitis* OR enteritis* OR ileitis*) AND ((trial* OR random*))) AND ((cannabis OR cannabinol OR cannabinoid* OR cannabidiol OR bhang OR hashish OR hemp OR marihuana OR marijuana OR nabilone OR cesamet OR tetrahydrocannabinol OR dronabinol OR levonantradol OR nabiximols OR palmidrol OR tetrahydrocannabinolic OR sativex OR endocannabinoid*))) AND ((publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb] OR pubstatusaheadofprint)))))) Sort by: Most Recent

Web of Science

10 #8 AND #9 1,871
 9 TS= clinical trial* OR TS=research design OR TS=comparative stud* OR TS=evaluation stud* OR TS=controlled trial* OR TS=follow-up stud* OR TS=prospective stud* OR TS=random* OR TS=placebo* OR TS=(single blind*) OR TS=(double blind*) 5,772,934
 8 #7 AND #1 7,146
 7 #6 OR #5 OR #4 OR #3 OR #2 1,648,139
 6 TS=(spasticity or spasm or spastic or hypertonia) 50,631
 5 TS= tmj OR TS= tmjd OR TS= IBS OR TS= crohn* OR TS= colitis* OR TS= enteritis* OR TS= ileitis* 185,102
 4 TS= arthrodyni* OR TS= myalgi* OR TS= myodyn* OR TS= ischialgi* OR TS= crps OR TS= brachialgia 13,911
 3 TS= headache* OR TS=fibromyalgi* OR TS= causalgia OR TS= radiculopathy* OR TS= whiplash OR TS= backache* OR TS= backpain* OR TS= dorsalgi* OR TS= arthralgi* OR TS= polyarthralgi* 129,034
 2 TS= pain* OR TS=osteoarthrit* OR TS= osteo-arthritis OR TS= arthrit* OR TS=neuropath* OR TS= neuralgi* OR TS=zoster* OR TS= migraine* 1,373,602
 1 TS=cannabis OR TS= cannabinol OR TS= cannabinoid* OR TS=cannabidiol OR TS=bhang OR TS=hashish OR TS= hemp OR TS=marihuana OR TS= marijuana OR TS= nabilone OR TS= cesamet OR TS= tetrahydrocannabinol OR TS= dronabinol OR TS= levonantradol OR TS= nabiximols OR TS= palmidrol OR TS=tetrahydrocannabinolic OR TS=sativex OR TS= endocannabinoid* 82,113

Cannabis-Med

International Association for Cannabinoid Medicines, database of clinical studies
<http://www.cannabis-med.org/studies/study.php>

Diagnosis: Pain or spasticity

AND

Study design: Controlled Study

Cannabinoids for chronic non-cancer pain (matrix of evidence)
<https://www.epistemonikos.org/en/matrixes/58f5158d7aac87666ca8853>
 97 Primary Studies
 Cannabis Spasticity
 45 Primary studies

eAppendix 2: Full reference list of eligible studies

(Studies reported 2 separate trials in one paper: Arai et al. 2015, and Tominaga et al 2016.)

1. Afilalo M, Etropolski MS, Kuperwasser B, et al. Efficacy and safety of Tapentadol extended release compared with oxycodone controlled release for the management of moderate to severe chronic pain related to osteoarthritis of the knee: a randomized, double-blind, placebo- and active-controlled phase III study. *Clin Drug Investig* 2010;30(8):489-505. doi: 10.2165/11533440-00000000-00000.
2. Andresen SR, Bing J, Hansen RM, et al. Ultramicronized palmitoylethanolamide in spinal cord injury neuropathic pain: a randomized, double-blind, placebo-controlled trial. *Pain* 2016;157(9):2097-103. doi: 10.1097/j.pain.0000000000000623 [published Online First: 2016/05/27]
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eAppendix 3: Reference list of studies excluded from quantitative analysis

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eTable 1. Psychometric studies for instruments used for measuring patient reported outcomes in eligible randomized controlled trials

| Outcome | Instruments and psychometric studies |
|-----------------------|---|
| Pain relief | 4-point categorical scale ¹ ; 5 point Likert scale ² ; Brief Pain Inventory ^{3,4} ; Multidimensional pain inventory (MPI-S) swedish version ⁵ ; Neuropathic Pain Scale ^{6,7} ; Short-form McGill Pain Questionnaire ³ ; Visual pain intensity scale ³ ; WOMAC Pain subscale ^{3,8} |
| Physical functioning | Back pain functional scale ⁹ ; Barthel index; BPI walking ability subscale ^{3,4} ; Disability Assessment Scale; Guy's Neurological Disability Scale (GNDS) ¹⁰ ; Oswestry Disability Index ^{11,12} ; Pain Disability Index ¹³ ; Roland Morris Disability Questionnaire ^{13,14} ; SF-12 PCS ¹⁵ ; Shortened Treatment Outcomes in Pain Survey instrument (S-TOPS) ¹⁶ ; WOMAC PF scale ^{3,8} |
| Emotional functioning | BPI mood subscale ^{3,4} ; General Health Questionnaire (GHQ-30); Profile of Mood states ³ ; VAS Bond and Lader mood ¹⁷ |
| Role functioning | Pain Disability Index ¹³ ; S-TOPS Role-emotional disability ¹⁶ |
| Social functioning | BPI relations with other people subscale ^{3,4} ; S-TOPS Family-social disability ¹⁶ |
| Sleep quality | BPI sleep ^{3,4} ; Medical Outcomes Study Sleep Scale ¹⁸ |

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eTable 2. Baseline characteristics of eligible randomized controlled trials (N = 90 RCTs)

| Author | Total # randomized | Pain condition | Age (year) | Sex (female%) | Duration of chronic pain(month) | # of arms | Interventions | Control | Length of follow-up (days) |
|-------------------------------|--------------------|--|------------|---------------|---------------------------------|-----------|--------------------------------|---------|----------------------------|
| Opioids versus placebo | | | | | | | | | |
| Afilalo (2010) | 1030 | Osteoarthritis | 58 | 61 | NR | 3 | Tapentadol-ER Oxycodone-ER | Placebo | 84 |
| Arai (2015) | 150 | Mixed neuropathic & non-neuropathic conditions | 66 | 67 | NR | 2 | Fentanyl-PATCH | Placebo | 84 |
| Arai (2015) | 163 | Mixed neuropathic | 66 | 49 | NR | 2 | Fentanyl-PATCH | Placebo | 84 |
| Babul (2004) | 246 | Osteoarthritis | 61 | 61 | 154 | 2 | Tramadol-ER | Placebo | 84 |
| Boureau (2003) | 127 | Postherpetic neuralgia | 66 | 62 | 6.7 | 2 | Tramadol-ER | Placebo | 42 |
| Breivik (2010) | 199 | Osteoarthritis | 50 | 58 | NR | 2 | Buprenorphine-PATCH | Placebo | 180 |
| Burch (2007) | 646 | Osteoarthritis | 62 | 63 | NR | 2 | Tramadol-ER | Placebo | 84 |
| Buynak (2010) | 981 | Low back pain | 50 | 58 | NR | 3 | Tapentadol-ER; Oxycodone-ER | Placebo | 105 |
| Caldwell (2002) | 295 | Osteoarthritis | 61 | 62 | NR | 4 | Morphine-ER | Placebo | 28 |
| Caldwell (1999) | 70 | Osteoarthritis | 57 | 53 | NR | 3 | Oxycodone-ER | Placebo | 28 |
| Christoph (2017) | 252 | neuropathic & non-neuropathic conditions | | 62 | NR | 5 | Tapentadol-ER | Placebo | 98 |
| Chu (2012) | 139 | Low back pain | 45 | 44 | NR | 2 | Morphine-ER | Placebo | 30 |
| DeLemos (2011) | 808 | Osteoarthritis | 60 | 100 | 96.7 | 2 | Tramadol-ER | Placebo | 84 |
| Fishman (2007) | 552 | Osteoarthritis | 61 | 62 | NR | 4 | Tramadol-ER | Placebo | 84 |
| Fleischmann (2001) | 129 | Osteoarthritis | 62 | 62 | 364 | 2 | Tramadol-NR | Placebo | 91 |
| Friedmann (2011) | 412 | Osteoarthritis | 58 | 70 | NR | 2 | Oxycodone-ER | Placebo | 84 |
| Gana (2006) | 1020 | Osteoarthritis | 58 | 62 | NR | 5 | Tramadol-ER | Placebo | 84 |
| Gilron (2005) | 57 | Postherpetic neuralgia & painful diabetic neuropathy | 50 | 56 | NR | 2 | Morphine-ER | Placebo | 28 |
| Gimbel (2003) | 159 | Painful diabetic neuropathy | | | 54.5 | 2 | Oxycodone-ER | Placebo | 42 |
| Gimbel (2016) | 511 | Low back pain | 59 | 48 | NR | 2 | Buprenorphine-Buccal | Placebo | 84 |
| Gordon (2010) | 78 | Low back pain | 54 | 47 | NR | 2 | Buprenorphine-PATCH | Placebo | 28 |
| Gordon (2010) | 79 | Mixed neuropathic & non-neuropathic conditions | 50 | 60 | 170 | 2 | Buprenorphine-PATCH | Placebo | 28 |

| | | | | | | | | | |
|-------------------|-----|-----------------------------|------|------|------|---|-----------------------------|---------|-----|
| Hale (2007) | 143 | Low back pain | 56 | 55 | NR | 2 | Oxymorphone-ER | Placebo | 84 |
| Hale (2010) | 268 | Low back pain | 48 | 50 | NR | 2 | Hydromorphone-ER | Placebo | 84 |
| Hale (2015) | 370 | Low back pain | 51 | 51 | NR | 2 | Hydrocodone-ER | Placebo | 84 |
| Harati (1998) | 131 | Painful diabetic neuropathy | 59 | 40 | NR | 2 | Tramadol-NR | Placebo | 42 |
| Huse (2001) | 12 | Phantom limb pain | 51 | 17 | NR | 2 | Morphine-ER | Placebo | 28 |
| Katz (2007) | 205 | Low back pain | 49 | 53 | NR | 2 | Oxymorphone-ER | Placebo | 84 |
| Katz (2015) | 389 | Low back pain | 49 | 53 | NR | 2 | Oxycodone-ER | Placebo | 84 |
| Khoromi (2007) | 55 | Lumbar radiculopathy | | | NR | 2 | Morphine-ER | Placebo | 49 |
| Kawamata (2019) | 130 | Low back pain | 53 | 45 | NR | 2 | Oxycodone-ER | Placebo | 49 |
| Langford (2006) | 399 | Osteoarthritis | 63 | 67 | NR | 2 | Fentanyl-PATCH | Placebo | 42 |
| Lin (2016) | 21 | Low back pain | 41.9 | 33 | 97.2 | 2 | Morphine-ER | Placebo | 30 |
| Ma (2008) | 116 | Chronic neck pain | 56 | 38 | NR | 2 | Oxycodone-ER | Placebo | 28 |
| Markenson (2005) | 107 | Osteoarthritis | 63 | 38 | NR | 2 | Oxycodone-ER | Placebo | 90 |
| Matsuimoto (2005) | 491 | Osteoarthritis | 63 | 62 | NR | 4 | Oxymorphone-ER Oxycodone-ER | Placebo | 28 |
| Mayorga (2016) | 98 | Osteoarthritis | 59 | 56 | NR | 4 | Oxycodone-ER | Placebo | 112 |
| Moran (1991) | 15 | Osteoarthritis | | 5 | NR | 2 | Morphine-ER | Placebo | 28 |
| Moulin (1996) | 61 | Chronic post-traumatic pain | 40 | 59 | 40.8 | 2 | Morphine-ER | Placebo | 77 |
| Munera (2010) | 315 | Osteoarthritis | 61 | 67 | NR | 2 | Buprenorphine-PATCH | Placebo | 28 |
| Niesters (2014) | 25 | Painful diabetic neuropathy | 63 | 41.6 | NR | 2 | Tapentadol-ER | Placebo | 28 |
| Norrbrink (2009) | 36 | Post-traumatic neuralgia | 51 | 78 | NR | 2 | Tramadol-NR | Placebo | 28 |
| Peloso (2000) | 103 | Osteoarthritis | 62 | 40 | NR | 2 | Codeine-ER | Placebo | 28 |
| Raja (2002) | 76 | Postherpetic neuralgia | | | NR | 2 | Morphine-ER | Placebo | 56 |
| Rauck (2013) | 990 | Osteoarthritis | 50 | 56 | NR | 3 | Hydromorphone-ER | Placebo | 84 |
| Rauck (2014) | 302 | Low back pain | 50 | 63 | NR | 2 | Hydrocodone-ER | Placebo | 84 |
| Rauck (2016) | 420 | Low back pain | 59 | 64 | NR | 2 | Buprenorphine-Buccal | Placebo | 84 |
| Russell (2000) | 69 | Fibromyalgia | 49 | 94 | NR | 2 | Tramadol-ER | Placebo | 42 |
| Schnitzer (2000) | 254 | Low back pain | 47 | 50 | NR | 2 | Tramadol-NR | Placebo | 28 |
| Schwartz (2011) | 395 | Painful diabetic neuropathy | 62 | 43 | 76 | 2 | Tapentadol-ER | Placebo | 84 |

| | | | | | | | | | |
|--|-----|--|------|-----|-------|---|-------------------------------|----------------|-----|
| Serrie (2017) | 990 | Osteoarthritis | 62 | 69 | NR | 3 | Tapentadol-ER Oxycodone-ER | Placebo | 105 |
| Simpson (2016) | 186 | Diabetic neuropathy | 63 | 33 | NR | 2 | Buprenorphine-PATCH | Placebo | 84 |
| Sindrup (1999) | | Painful diabetic neuropathy | 57 | 24 | 36 | | Tramadol-ER | Placebo | 28 |
| Sindrup (2012) | 64 | Painful polyneuropathy | | | NR | 3 | Tramadol-ER | Placebo | 28 |
| Steiner (2011) | 541 | Low back pain | 49 | 55 | 108.6 | 2 | Buprenorphine-PATCH | Placebo | 84 |
| Thorne (2008) | 100 | Osteoarthritis | 61 | 55 | NR | 2 | Tramadol-ER | Placebo | 28 |
| Tominaga (2016) | 91 | neuropathic & non-neuropathic conditions | | | NR | 2 | Tapentadol-ER | Placebo | 84 |
| Tominaga (2016) | 91 | Postherpetic neuralgia & painful diabetic neuropathy | | | NR | 2 | Tapentadol-ER | Placebo | 84 |
| Uberall (2012) | 240 | Low back pain | | | NR | 2 | Tramadol-ER | Placebo | 28 |
| Vinik (2014) | 320 | Painful diabetic neuropathy | 58 | 41 | NR | 2 | Tapentadol-ER | Placebo | 84 |
| Vojtassak (2011) | 288 | Osteoarthritis | 66 | 72 | NR | 2 | Hydromorphone-ER | Placebo | 112 |
| Vorsanger (2008) | 386 | Low back pain | 47 | 50 | NR | 3 | Tramadol-ER | Placebo | 84 |
| Watson (1998) | 50 | Postherpetic neuralgia | 70 | 44 | 31 | 2 | Oxycodone-ER | placebo | 28 |
| Webster (2006) | 307 | Low back pain | 48 | 61 | NR | 4 | Oxycodone-ER | Placebo | 84 |
| Wen (2015) | 588 | Low back pain | 48 | 57 | NR | 2 | Hydrocodone | Placebo | 84 |
| Wu (2008) | 60 | postamputation | 63 | 21 | 51.3 | 2 | Morphine-ER | Placebo | 42 |
| Opioids versus cannabis for medical use | | | | | | | | | |
| Frank 2008 | 192 | Neuropathic pain | 50 | 26 | 76.4 | 2 | THC, Nabilone | Dihydrocodeine | 42 |
| Cannabis for medical use versus placebo | | | | | | | | | |
| Andresen (2016) | 73 | Spinal cord injury-related neuropathic pain | 56 | 26 | ≥3 | 2 | PEA | Placebo | 84 |
| Blake (2006) | 58 | Rheumatoid arthritis pain | 63 | 79 | NR | 2 | THC/CBD, Nabiximols | Placebo | 48 |
| de Vries (2017) | 65 | Chronic abdominal pain | 53 | 39 | ≥3 | 2 | THC, Namisol | Placebo | 51 |
| Eibach (2020) | 68 | HIV associated neuropathic pain | 50 | 6 | 157.2 | 2 | Cannabidiol (CBDV) | Placebo | 28 |
| Germimi (2017) | 20 | Mixed chronic noncancer pain | 83 | 100 | ≥6 | 2 | PEA | Placebo | 42 |
| Hunter (2018) | 320 | Osteoarthritis | 62 | 51 | ≥12 | 2 | CBD synthetic gel | Placebo | 84 |
| Langford (2013) | 339 | Multiple sclerosis central pain | 49 | 68 | 65.5 | 2 | THC/CBD, Nabiximols | Placebo | 98 |
| Markova (2018) | 106 | Multiple sclerosis with pain (no details) | 51.3 | 80 | 170.4 | 2 | THC/CBD, Nabiximols | Placebo | 84 |

| | | about pain condition) | | | | | | |
|-------------------------|-----|--|------|----|-------|---|---------------------|-------------|
| NCT00710424 (2006) | 297 | Diabetic neuropathy | 60 | 38 | ≥6 | 2 | THC/CBD, Nabiximols | Placebo 98 |
| Novotna (2011) | 241 | Multiple sclerosis with pain (no details about pain condition) | 49 | 60 | 151.2 | 2 | THC/CBD, Nabiximols | Placebo 84 |
| Nurmikko (2007) | 125 | Peripheral neuropathic pain | 53 | 59 | 75.6 | 2 | THC/CBD, Nabiximols | Placebo 35 |
| Pinsger (2006) | 60 | Refractory pain related to musculoskeletal system | 55 | 77 | 240 | 2 | THC, Nabilone | Placebo 30 |
| Rog (2005) | 66 | Multiple sclerosis central pain | 49 | 79 | 138.8 | 2 | THC/CBD | Placebo 28 |
| Schimrigk (2017) | 240 | Multiple sclerosis central pain | 48 | 73 | NR | 2 | THC, Marinol | Placebo 112 |
| Selvarajah (2010) | 30 | Diabetic neuropathy | 56 | 37 | NR | 2 | THC/CBD, Nabiximols | Placebo 84 |
| Serpell (2014) | 246 | Peripheral neuropathy | 57 | 61 | 75.6 | 2 | THC/CBD, Nabiximols | Placebo 98 |
| Skrabek (2008) | 40 | Fibromyalgia | 49 | NR | NR | 2 | THC, Nabilone | Placebo 28 |
| Toth (2012) | 26 | Diabetic neuropathy | 61 | 46 | 85.8 | 2 | THC, Nabilone | Placebo 35 |
| van Amerongen (2018) | 24 | Multiple sclerosis neuropathic pain and spasticity | 54 | 6 | 137.4 | 2 | THC, Namisol | Placebo 28 |
| Wissel (2006) | 26 | Chronic upper motor neuron syndrome | 44.8 | 69 | NR | 2 | THC, Nabilone | Placebo 28 |
| Xu (2020) | 29 | Peripheral neuropathic pain | 68 | 38 | ≥3 | 2 | CBD | Placebo 28 |
| Zajicek (2003 and 2005) | 657 | Multiple sclerosis with pain (no details about pain condition) | 51 | 63 | NR | 2 | THC/CBD, Marinol | Placebo 112 |
| Zajicek (2012) | 279 | Multiple sclerosis with pain (no details about pain condition) | 52 | 63 | NR | 2 | THC/CBD | Placebo 84 |

eTable 3. Risk of bias assessment of the eligible randomized controlled trials (N = 90 RCTs)

| Study | Loss to follow-up (%) | Randomization | Concealment | Blinding of patients | Blinding of care providers | Blinding of data collectors | Blinding of outcome assessors |
|------------------|-----------------------|--------------------------|-----------------------------------|----------------------|----------------------------|-----------------------------|-------------------------------|
| Afilalo 2010 | 51 | adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Andresen 2016 | 15 | Adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Arai 2015a | 49 | inadequate randomization | inadequate allocation concealment | Yes | Yes | Yes | Yes |
| Arai 2015b | 54 | inadequate randomization | inadequate allocation concealment | Yes | Yes | Yes | Yes |
| Babul 2004 | 50 | adequate randomization | inadequate allocation concealment | Yes | Yes | Yes | Yes |
| Blake 2006 | 7 | Adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Boureau 2003 | 15 | adequate randomization | inadequate allocation concealment | Yes | Yes | Yes | Yes |
| Breivik 2010 | 44 | adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Burch 2007 | 24 | adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Buynak 2010 | 53 | adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Caldwell 1999 | 34 | inadequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Caldwell 2002 | 38 | inadequate randomization | inadequate allocation concealment | Yes | Yes | Yes | Yes |
| Christoph 2017 | 30 | adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Chu 2012 | 26 | inadequate randomization | inadequate allocation concealment | Yes | No | Yes | Yes |
| de Vries 2017 | 25 | Inadequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| DeLemos 2011 | 48 | inadequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Eibach 2020 | 18 | adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Fishman 2007 | 44 | adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Fleischmann 2001 | 71 | adequate randomization | inadequate allocation concealment | Yes | Yes | Yes | Yes |
| Frank 2008 | 24 | Adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Friedmann 2011 | 36 | inadequate randomization | inadequate allocation concealment | Yes | Yes | Yes | Yes |
| Gana 2006 | 45 | adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |

| | | | | | | | |
|----------------|----|--------------------------|-----------------------------------|-----|-----|-----|-----|
| Germini 2017 | 30 | Adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Gilron 2005 | 9 | inadequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Gimbel 2003 | 28 | adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Gimbel 2016 | 31 | inadequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Gordon 2010a | 35 | adequate randomization | inadequate allocation concealment | Yes | Yes | Yes | Yes |
| Gordon 2010b | 37 | adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Hale 2007 | 53 | inadequate randomization | inadequate allocation concealment | Yes | Yes | Yes | Yes |
| Hale 2010 | 59 | adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Hale 2015 | 20 | adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Harati 1998 | 37 | adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Hunter 2018 | 26 | Inadequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Huse 2001 | 17 | inadequate randomization | inadequate allocation concealment | No | No | No | No |
| Katz 2007 | 42 | inadequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Katz 2015 | 43 | adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Kawamata 2019 | 37 | adequate randomization | inadequate allocation concealment | Yes | Yes | Yes | Yes |
| Khoromi 2007 | 33 | adequate randomization | inadequate allocation concealment | Yes | Yes | Yes | Yes |
| Langford 2006 | 52 | adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Langford 2013 | 12 | Adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Lin 2016 | 0 | inadequate randomization | inadequate allocation concealment | Yes | Yes | Yes | Yes |
| Ma 2008 | 90 | inadequate randomization | inadequate allocation concealment | Yes | Yes | Yes | Yes |
| Markenson 2005 | 66 | adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Markova 2018 | 9 | Inadequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Matsumoto 2005 | 45 | adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Mayorga 2016 | 61 | adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Moran 1991 | 25 | inadequate randomization | inadequate allocation concealment | Yes | Yes | Yes | Yes |

| | | | | | | | |
|------------------|----|--------------------------|-----------------------------------|-----|-----|-----|-----|
| Moulin 1996 | 25 | inadequate randomization | inadequate allocation concealment | Yes | Yes | Yes | Yes |
| Munera 2010 | 51 | inadequate randomization | inadequate allocation concealment | Yes | Yes | Yes | Yes |
| NCT00710424 2006 | 23 | Inadequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Niesters 2014 | 0 | adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Norrbrink 2009 | 36 | inadequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Novotna 2011 | 7 | Inadequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Nurmikko 2007 | 16 | Adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Peloso 2000 | 36 | inadequate randomization | inadequate allocation concealment | Yes | Yes | Yes | Yes |
| Pinsger 2006 | 30 | Inadequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Raja 2002 | 42 | adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Rauck 2013 | 51 | inadequate randomization | inadequate allocation concealment | Yes | Yes | Yes | No |
| Rauck 2014 | 39 | inadequate randomization | adequate allocation concealment | Yes | Yes | No | No |
| Rauck 2016 | 9 | inadequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Rog 2005 | 3 | Adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Russell 2000 | 1 | adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Schimrigk 2017 | 26 | Adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Schnitzer 2000 | 43 | adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Schwartz 2011 | 33 | adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Selvarajah 2010 | 20 | Inadequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Serpell 2014 | 30 | adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Serrie 2017 | 46 | adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Simpson 2016 | 33 | adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Sindrup 1999 | 20 | inadequate randomization | inadequate allocation concealment | Yes | Yes | Yes | Yes |
| Sindrup 2012 | 8 | adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Skrabek 2008 | 18 | Adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |

| | | | | | | | |
|---------------------|----|--------------------------|-----------------------------------|-----|-----|-----|-----|
| Steiner 2011 | 32 | inadequate randomization | inadequate allocation concealment | Yes | Yes | Yes | Yes |
| Thorne 2008 | 25 | inadequate randomization | inadequate allocation concealment | Yes | Yes | Yes | Yes |
| Tominaga 2016a | 13 | inadequate randomization | inadequate allocation concealment | Yes | Yes | Yes | Yes |
| Tominaga 2016b | 9 | inadequate randomization | inadequate allocation concealment | Yes | Yes | Yes | Yes |
| Toth 2012 | 4 | Adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Uberall 2012 | 25 | adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| van Amerongen 2018 | 4 | Adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Vinik 2014 | 29 | adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Vojtassak 2011 | 31 | adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Vorsanger 2008 | 38 | adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Watson 1998 | 22 | inadequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Webster 2006 | 54 | adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Wen 2015 | 25 | inadequate randomization | inadequate allocation concealment | Yes | Yes | Yes | Yes |
| Wissel 2006 | 15 | Inadequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Wu 2008 | 41 | Adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Xu 2020 | 21 | Adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Zajicek 2003 & 2005 | 4 | Adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |
| Zajicek 2012 | 20 | Adequate randomization | adequate allocation concealment | Yes | Yes | Yes | Yes |

eTable 4. Network estimates and their certainty in evidence (GRADE) evaluating the effects of opioid and cannabis for medical use therapy in patients with chronic non-cancer pain across different outcomes

| Outcome | Comparison | Direct Estimate MD (95% CI) | Indirect Estimate MD (95% CI) | Network Estimate* MD (95% CrI)) | GRADE |
|--|-------------------------------------|--------------------------------|----------------------------------|------------------------------------|-----------------------|
| Pain (VAS 0-10) | Opioid vs placebo | -0.84 (-0.99, -0.69) | -0.83 (-0.97, -0.70) | -0.83 (-0.97, -0.70) | Moderate ² |
| | Cannabis for medical use vs placebo | -0.63 (-0.94, -0.32) | -0.59 (-0.88, -0.32) | -0.60 (-0.87, -0.33) | Low ^{2,8} |
| | Cannabis for medical use vs opioid | 0.13 (-0.54, 0.80) | 0.24 (-0.07, 0.55) | 0.23 (-0.06, 0.53) | Low ^{1,8} |
| Physical function (SF 0-100) | Opioid vs placebo | 2.38 (1.05, 3.72) | — | 2.05 (1.01, 3.29) | Moderate ⁸ |
| | Cannabis for medical use vs placebo | 3.00 (0.08, 5.91) | — | 2.52 (0.37, 4.91) | Moderate ⁸ |
| | Cannabis for medical use vs opioid | — | 0.47 (-1.97, 2.99) | 0.47 (-1.97, 2.99) | Moderate ² |
| Emotional function (SF 0-100) | Opioid vs placebo | -0.00 (-1.09, 1.09) | — | -0.15 (-1.10, 0.92) | High |
| | Cannabis for medical use vs placebo | 0.72 (-1.01, 2.45) | — | 0.70 (-1.42, 2.84) | Moderate ⁸ |
| | Cannabis for medical use vs opioid | — | 0.85 (-1.55, 3.18) | 0.85 (-1.55, 3.18) | Low ^{2,8} |
| Role function (SF 0-100) | Opioid vs placebo | 0.91 (-1.17, 2.98) | — | 0.94 (-1.26, 3.17) | Moderate ⁸ |
| | Cannabis for medical use vs placebo | 1.27 (-12.39, 14.93) | — | 0.88 (-3.78, 6.05) | Moderate ⁸ |
| | Cannabis for medical use vs opioid | — | -0.05 (-5.16, 5.60) | -0.05 (-5.16, 5.60) | Moderate ⁸ |
| Social function (SF 0-100) | Opioid vs placebo | 0.47 (-1.47, 2.41) | — | 1.17 (-1.72, 4.58) | Moderate ⁸ |
| | Cannabis for medical use vs placebo | -1.82 (-5.79, 2.15) | — | 1.70 (-3.28, 8.13) | Moderate ⁸ |
| | Cannabis for medical use vs opioid | — | 0.55 (-5.34, 7.41) | 0.55 (-5.34, 7.41) | Moderate ⁸ |
| Sleep quality (0-100) | Opioid vs placebo | 5.55 (2.67, 8.43) | — | 5.46 (2.62, 8.59) | Moderate ² |
| | Cannabis for medical use vs placebo | 6.04 (1.43, 10.66) | — | 5.95 (1.82, 10.24) | Low ^{2,8} |
| | Cannabis for medical use vs opioid | — | 0.49 (-4.72, 5.59) | 0.49 (-4.72, 5.59) | Low ^{2,8} |
| Outcome | Comparison | Direct Estimate OR (95% CI) | Indirect Estimate OR (95% CI) | Network Estimate* OR (95% CI) | GRADE |
| Discontinuations due to adverse events (enriched) | Opioid vs placebo | 1.39 (1.04, 1.86) | — | 1.25 (0.91, 1.67) | Low ^{1,8} |
| | Cannabis for medical use vs placebo | 5.00 (0.25, 101.7) | — | 0.96 (0.09, 10.80) | Low ^{1,8} |
| | Cannabis for medical use vs opioid | — | 0.77 (0.07, 8.83) | 0.77 (0.07, 8.83) | Low ^{1,8} |
| Discontinuations due to adverse events (non-enriched) | Opioid vs placebo | 3.58 (3.00, 4.27) | 3.27 (2.70, 3.93) | 3.27 (2.71, 3.90) | Moderate ¹ |
| | Cannabis for medical use vs placebo | 2.47 (1.49, 4.11) | 1.78 (1.15, 2.63) | 1.80 (1.19, 2.63) | High |
| | Cannabis for medical use vs opioid | 0.50 (0.16, 1.61) | 0.54 (0.34, 0.84) | 0.55 (0.36, 0.83) | Moderate ¹ |

* Imprecision only incorporated at network level not at direct or indirect.

Abbreviations: MD: Mean difference; 95 CI%: 95% Confidence Intervals; GRADE Certainty of Evidence.

GRADE Assessment: Reasons for downgrading direct evidence:

1. Rated down due to risk of bias
2. Rated down due to inconsistency
3. Rated down due to imprecision (effects were rated down if the associated measure of precision included no effect [a mean difference of 0])
4. Rated down due to indirectness
5. Rated down due to publication bias

Reasons for downgrading indirect evidence:

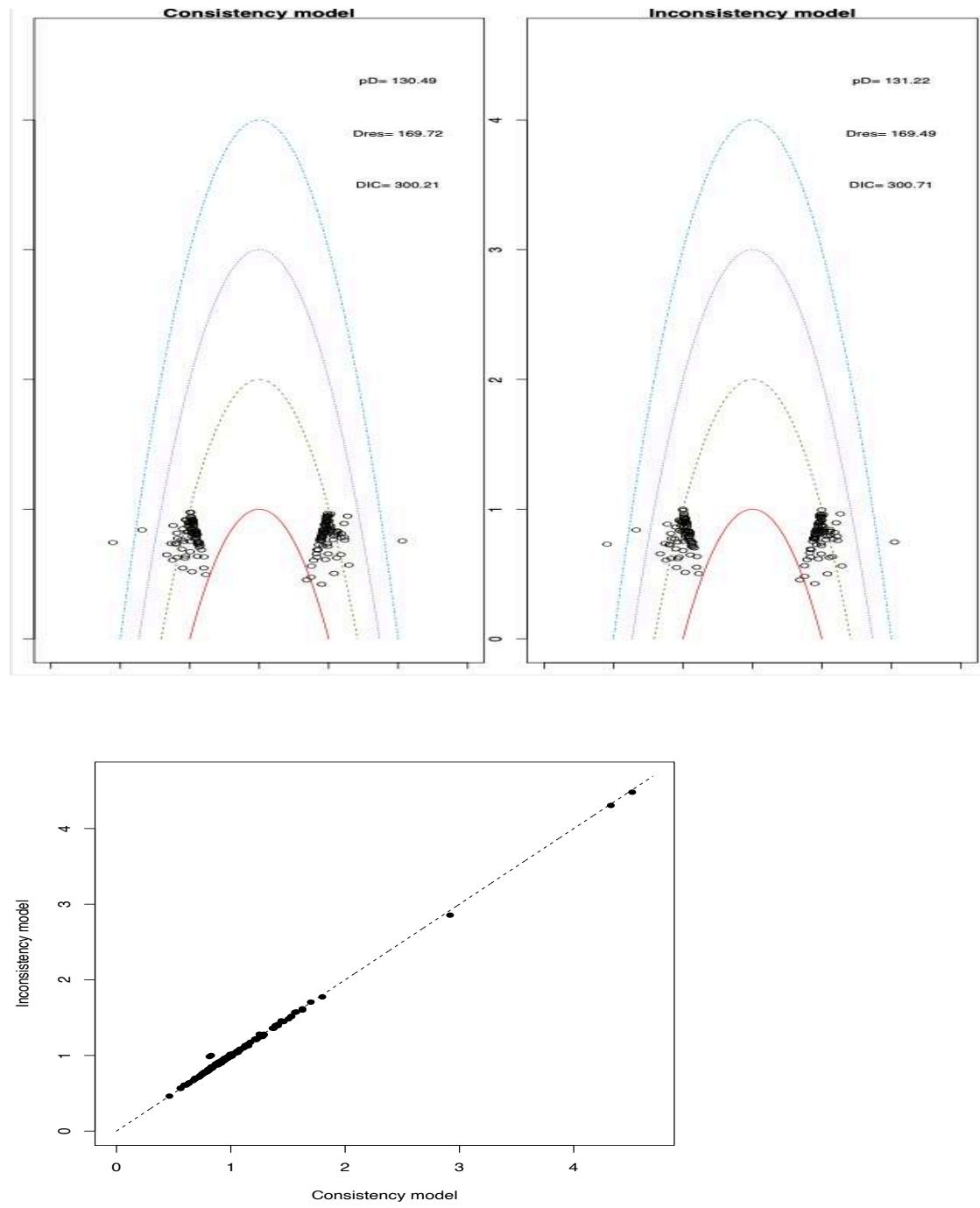
6. Rated down for intransitivity

Reasons for downgrading network evidence

7. Rated down due to incoherence

8. Rated down due to imprecision (either due to inclusion of the null value in the 95%CI, or because the evidence is provided by a small number of patients – a total number of patients less than the optimal information size [n=300])

When two of the same superscripts are listed with an estimate of treatment effect (e.g. ^{1,1}), this means the certainty of evidence (GRADE) was downgraded for 2 levels (-2), instead of one (-1)

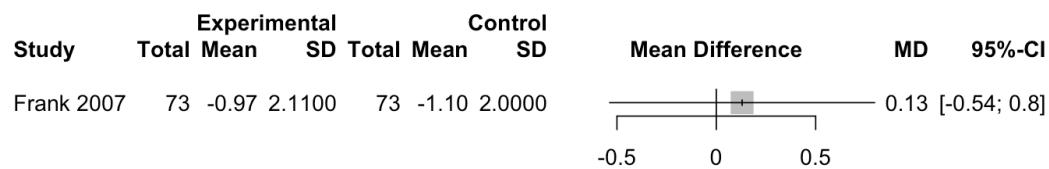
eFigure 1. Pain, random effects consistency and inconsistency model

eTable 5. Pain, node splitting outputs

Comparison of direct versus indirect evidence - Mean change in pain VAS from baseline

| Comparisons | Direct evidence | Indirect evidence |
|--------------------------------------|--------------------|--------------------|
| Cannabis for medical use vs. Opioids | 0.13 (-0.54, 0.80) | 0.23 (-0.10, 0.55) |

P-value = 0.792

Direct evidence forest plot

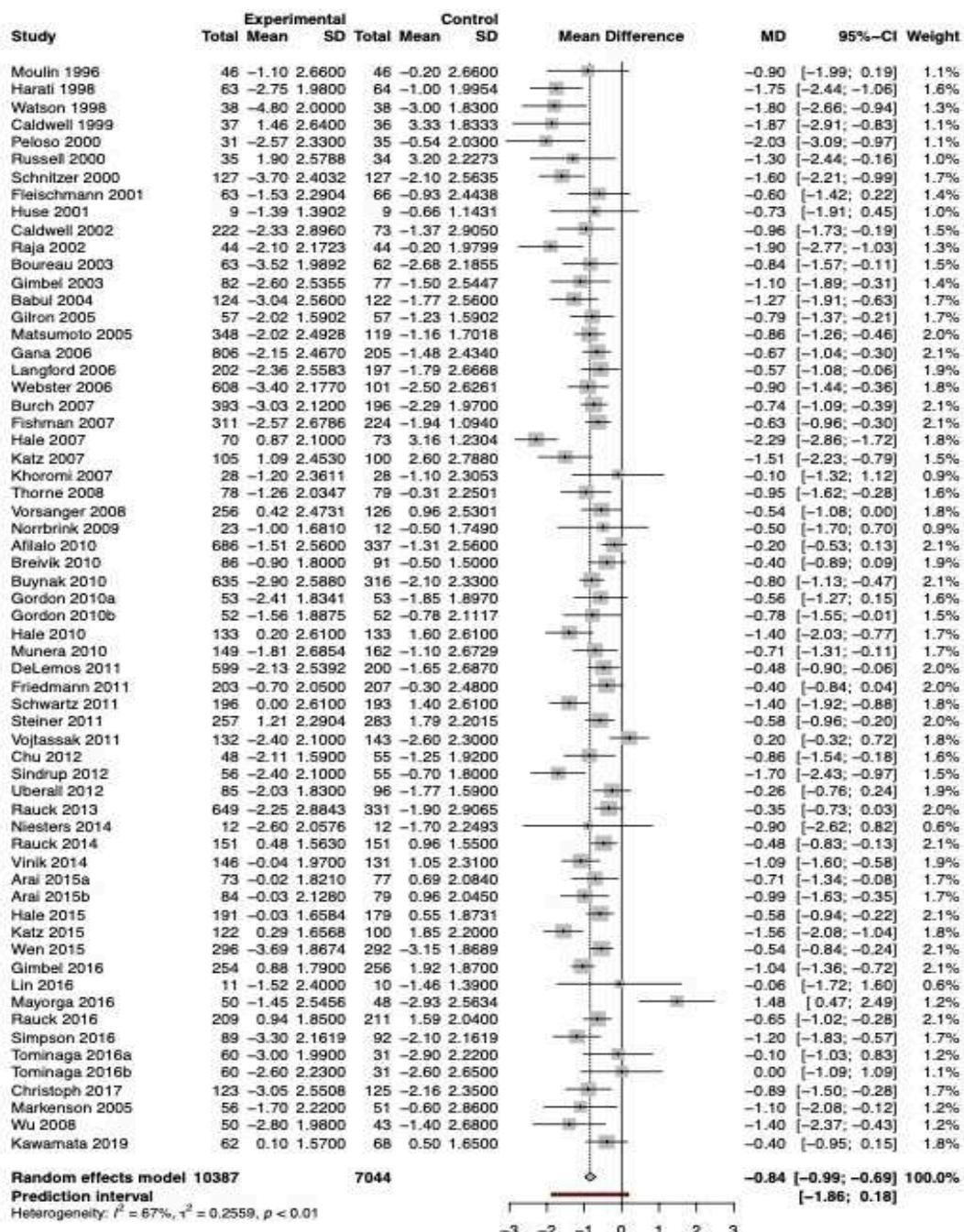
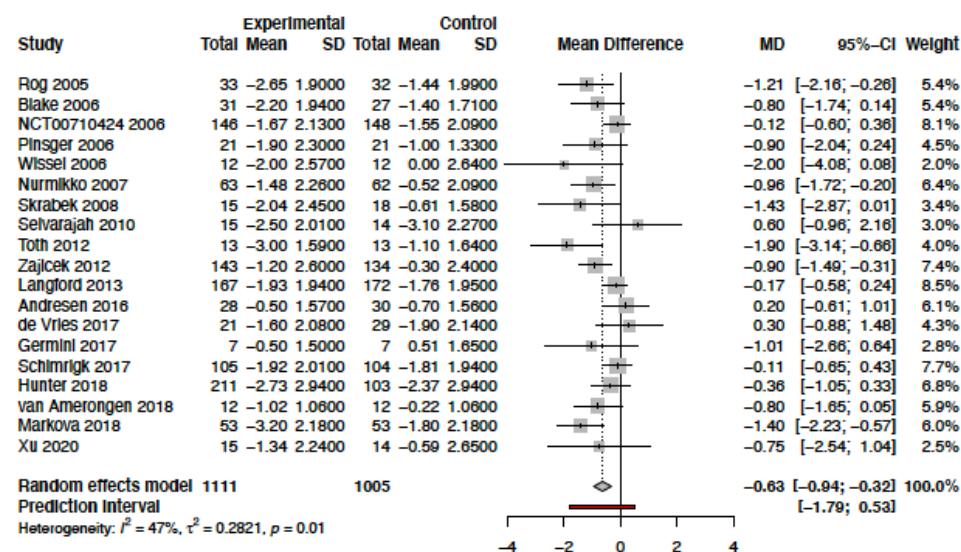
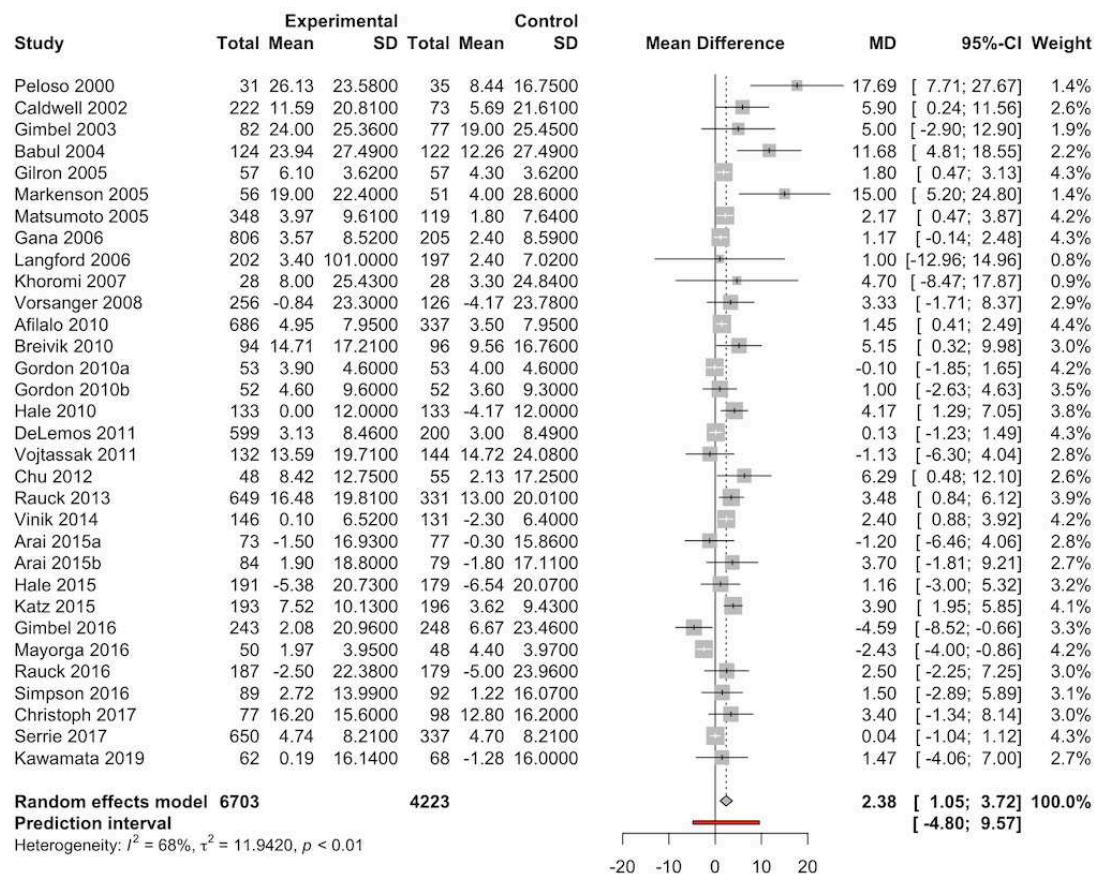
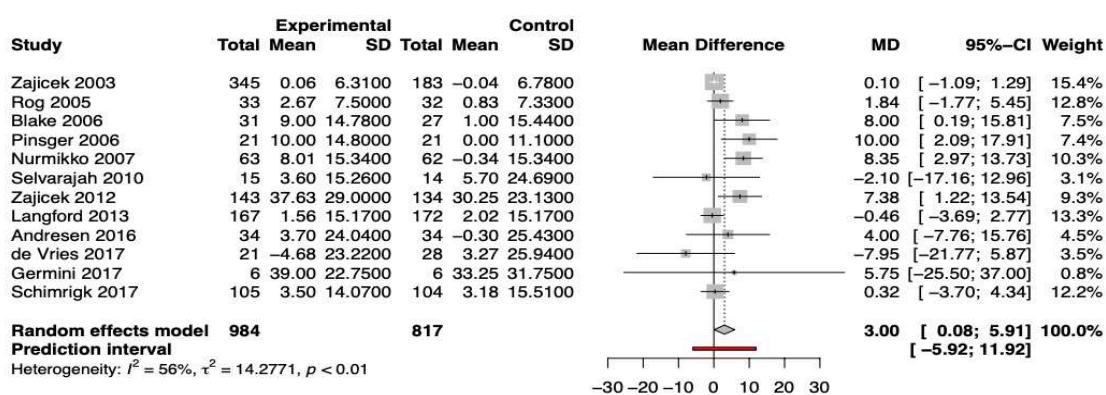
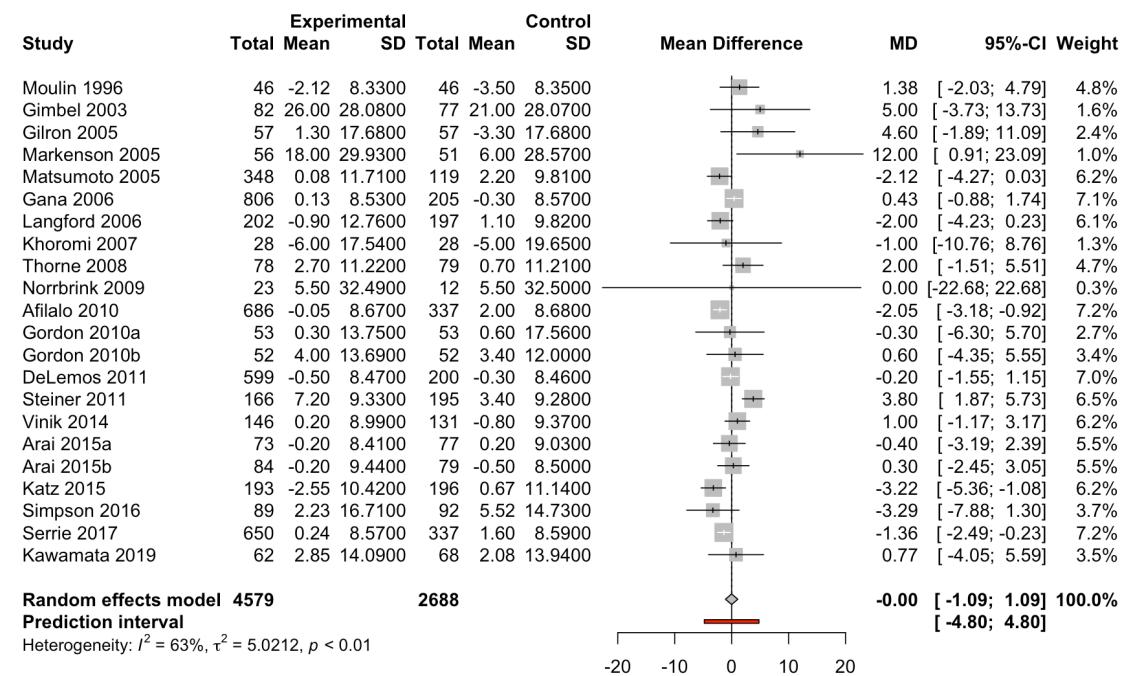
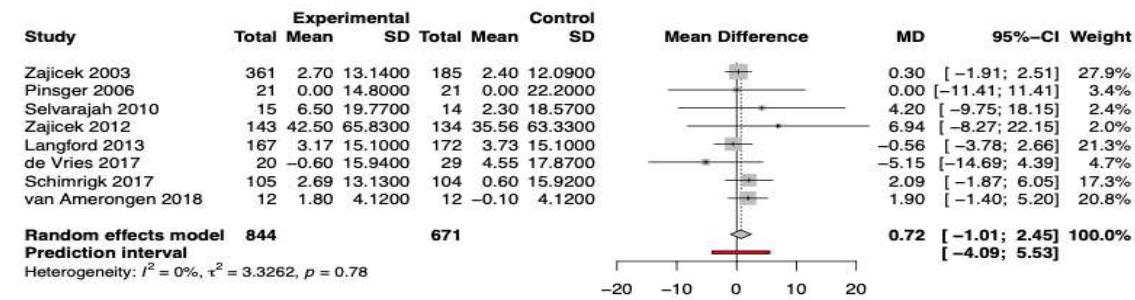
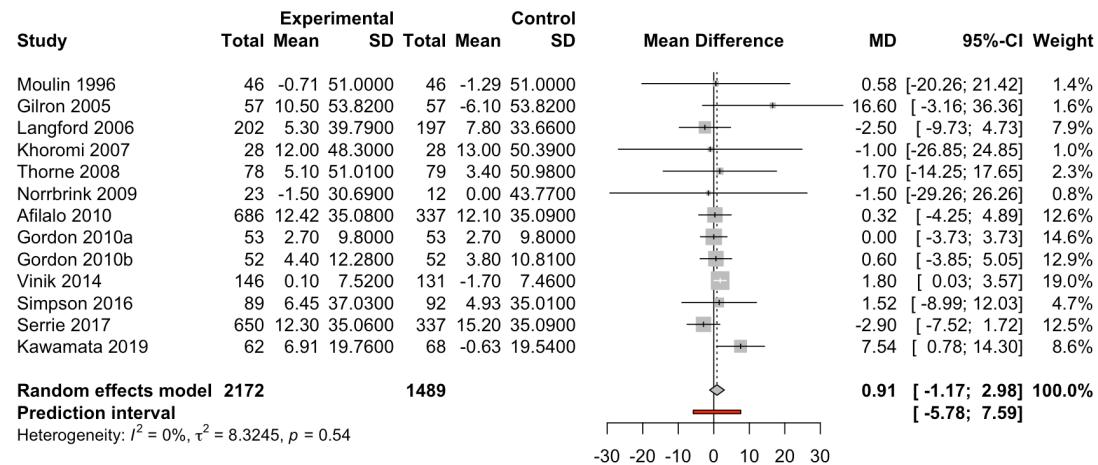
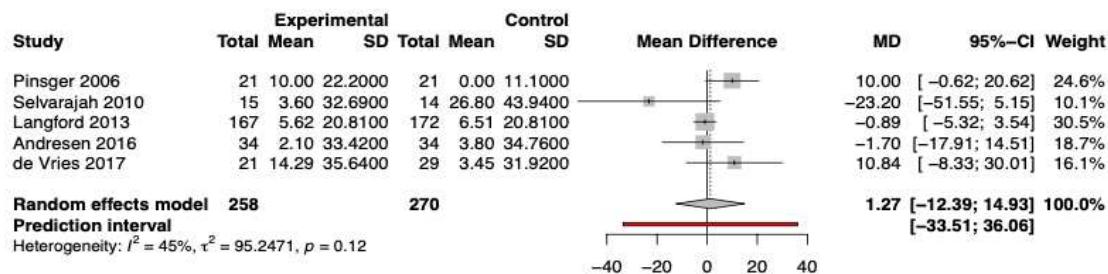
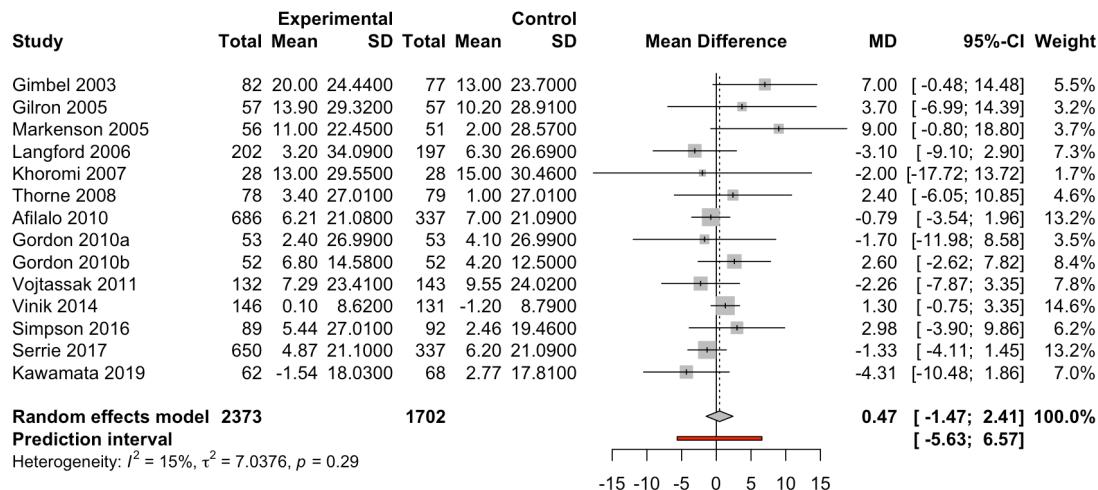
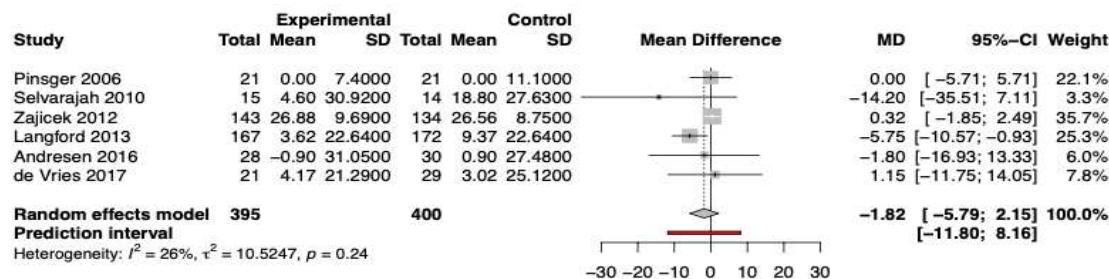
eFigure 2. Pain, opioids versus placebo pairwise meta-analysis random effect model

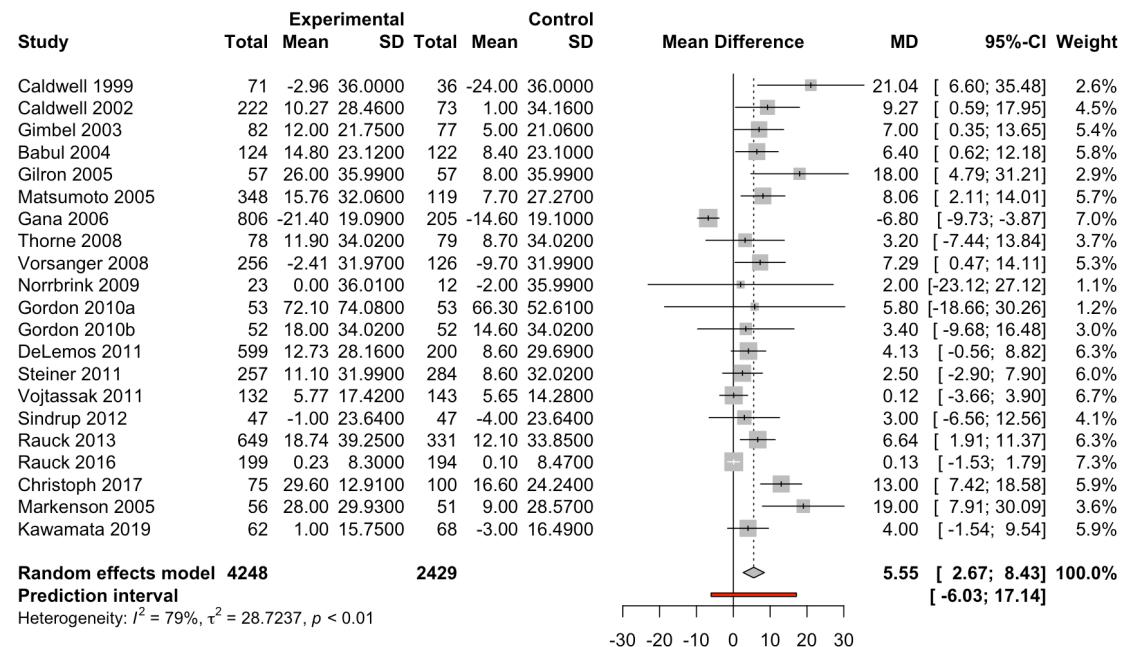
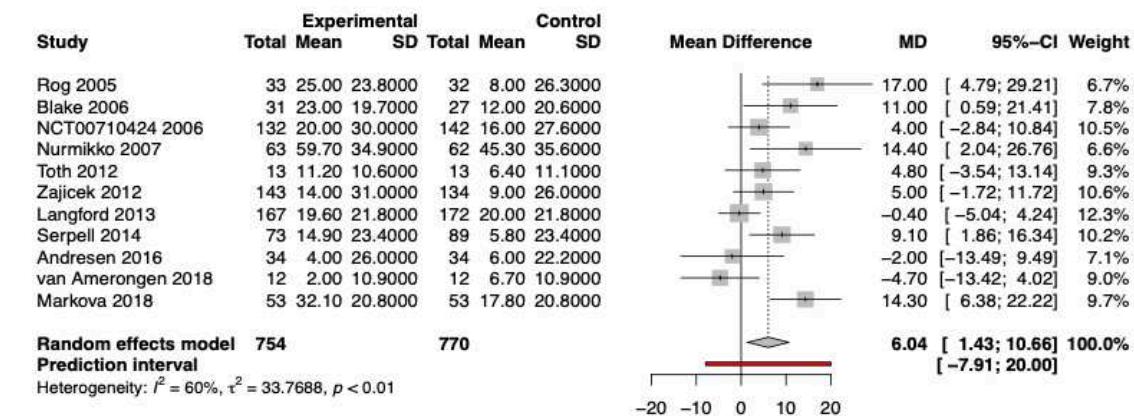
Figure 3. Pain, cannabis for medical use versus placebo pairwise meta-analysis random effects model

eFigure 4. Physical functioning, opioids versus placebo pairwise meta-analysis random effect model**eFigure 5. Physical functioning, cannabis for medical use versus placebo pairwise meta-analysis random effect model**

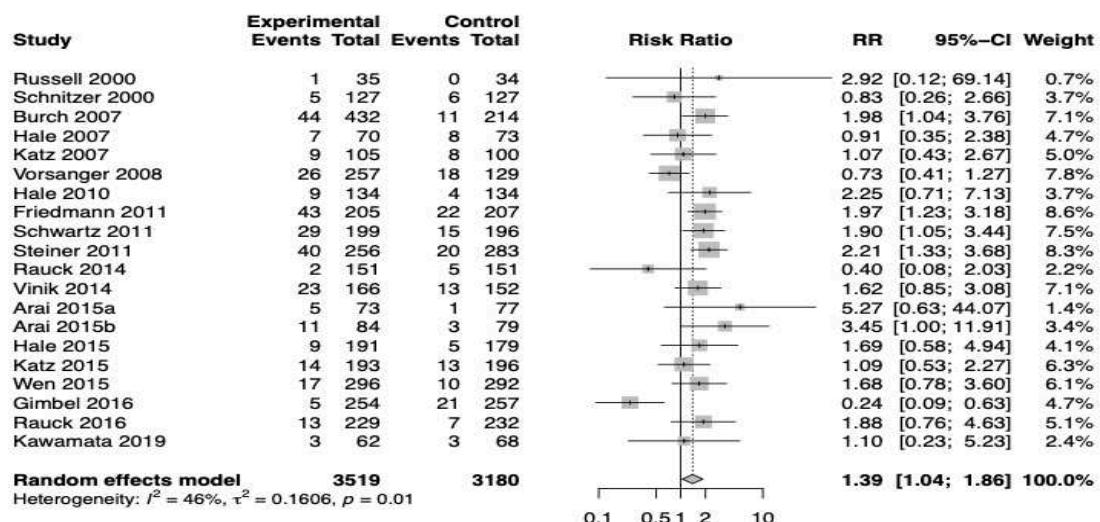
eFigure 6. Emotional functioning, opioids versus placebo pairwise meta-analysis random effect model**eFigure 7. Emotional functioning, cannabis for medical use versus placebo pairwise meta-analysis random effect model**

eFigure 8. Role functioning, opioids versus placebo pairwise meta-analysis random effect model**eFigure 9. Role functioning, cannabis for medical use versus placebo pairwise meta-analysis random effect model**

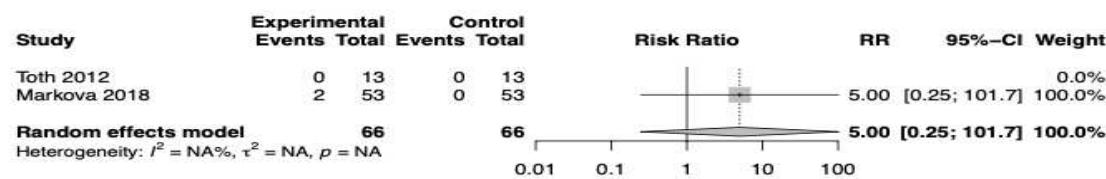
eFigure 10. Social functioning, opioids versus placebo pairwise meta-analysis random effect model**eFigure 11. Social functioning, cannabis for medical use versus placebo pairwise meta-analysis random effect model**

eFigure 12. Sleep quality, opioids versus placebo pairwise meta-analysis random effect model**eFigure 13. Sleep quality, cannabis for medical use versus placebo pairwise meta-analysis random effect model**

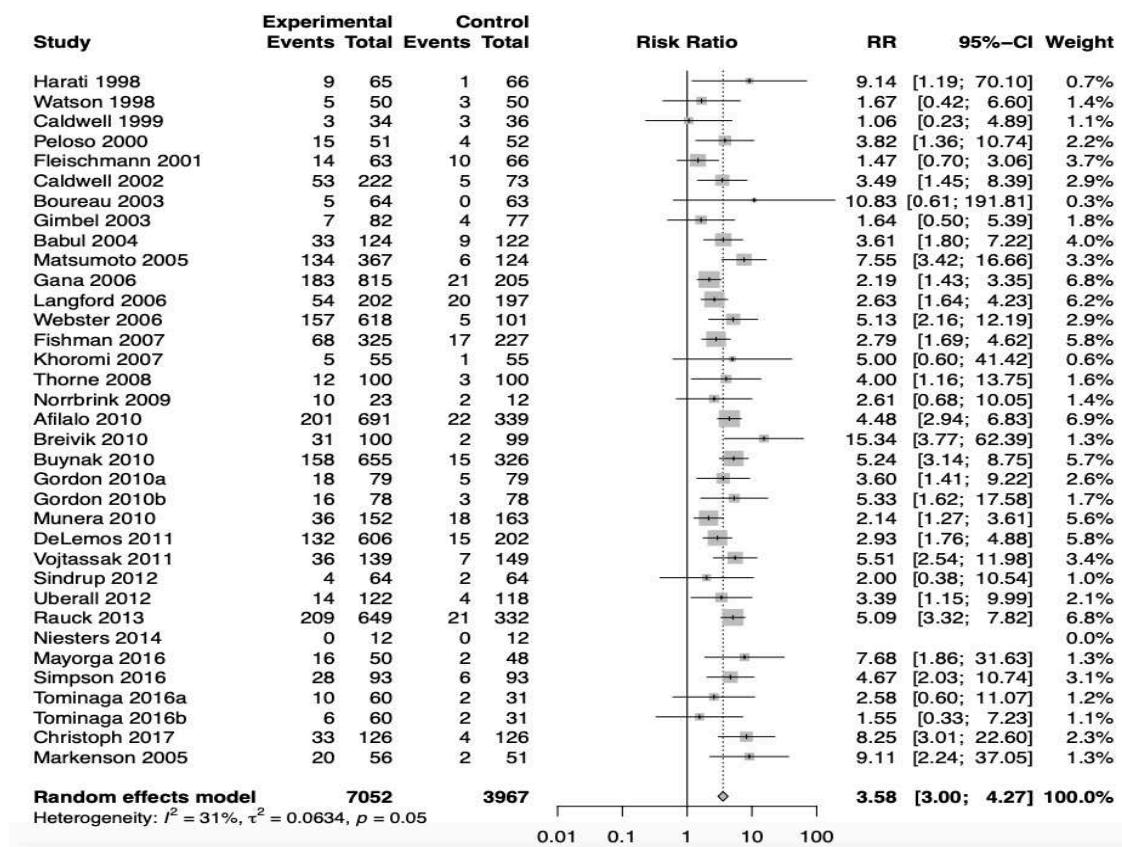
eFigure 14. Discontinuations due to adverse events (enriched trials), opioids versus placebo pairwise meta-analysis random effect model



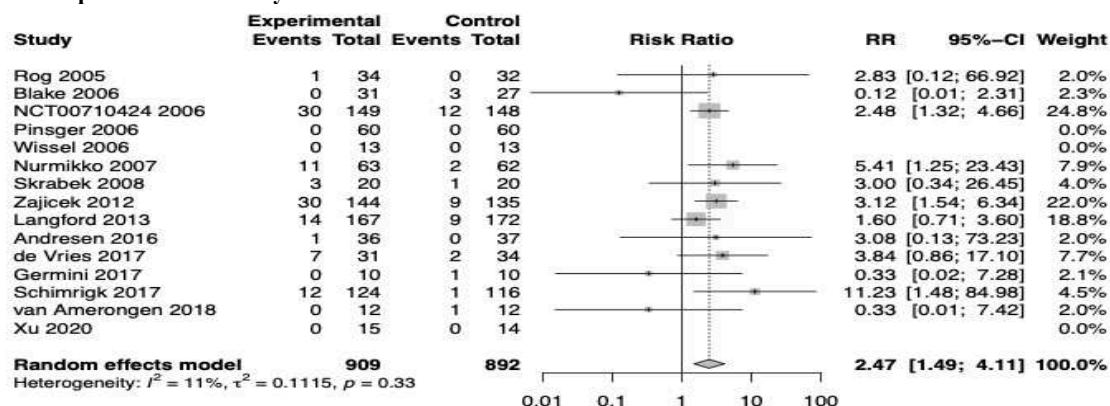
eFigure 15. Discontinuations due to adverse events (enriched trials), cannabis for medical use versus placebo pairwise meta-analysis random effect model



eFigure 16. Discontinuations due to adverse events (non-enriched trials), opioids versus placebo pairwise meta-analysis random effect model



eFigure 17. Discontinuations due to adverse events (non-enriched trials), cannabis for medical use versus placebo pairwise meta-analysis random effect model



Appendix 4: Reference list of cannabis for medical use studies with incomplete EQ-5D and SF-36 general health data**EQ-5D:**

1. Langford RM, Mares J, Novotna A, et al. A double-blind, randomized, placebo-controlled, parallel- group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. *J Neurol* 2013;260(4):984-97. doi: 10.1007/s00415-012-6739-4 [published Online First: 2012/11/28]
2. Novotna A, Mares J, Ratcliffe S, et al. A randomized, double-blind, placebo-controlled, parallel- group, enriched-design study of nabiximols* (Sativex((R))), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis. *Eur J Neurol* 2011;18(9):1122-31. doi: 10.1111/j.1468-1331.2010.03328.x [published Online First: 2011/03/03]
3. NCT00710424. A Study of Sativex® for Pain Relief Due to Diabetic Neuropathy: <https://ClinicalTrials.gov/show/NCT00710424>, 2006.
4. Selvarajah D, Gandhi R, Emery CJ, et al. Randomized placebo-controlled double-blind clinical trial of cannabis-based medicinal product (Sativex) in painful diabetic neuropathy: depression is a major confounding factor. *Diabetes Care* 2010;33(1):128-30. doi: 10.2337/dc09-1029 [published Online First: 2009/10/08]
5. Toth C, Mawani S, Brady S, et al. An enriched-enrolment, randomized withdrawal, flexible-dose, double-blind, placebo-controlled, parallel assignment efficacy study of nabilone as adjuvant in the treatment of diabetic peripheral neuropathic pain. *Pain* 2012;153(10):2073-82. doi: 10.1016/j.pain.2012.06.024 [published Online First: 2012/08/28]

SF-36 General health:

1. Frank B, Serpell MG, Hughes J, et al. Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain: randomised, crossover, double blind study. *BMJ* 2008;336(7637):199-201. doi: 10.1136/bmj.39429.619653.80 [published Online First: 2008/01/10]
2. Langford RM, Mares J, Novotna A, et al. A double-blind, randomized, placebo-controlled, parallel- group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. *J Neurol* 2013;260(4):984-97. doi: 10.1007/s00415-012-6739-4 [published Online First: 2012/11/28]
3. Markova J, Essner U, Akmaz B, et al. Sativex((R)) as add-on therapy vs. further optimized first-line ANTispastics (SAVANT) in resistant multiple sclerosis spasticity: a double-blind, placebo-controlled randomised clinical trial. *Int J Neurosci* 2019;129(2):119-28. doi: 10.1080/00207454.2018.1481066 [published Online First: 2018/05/25]
4. Novotna A, Mares J, Ratcliffe S, et al. A randomized, double-blind, placebo-controlled, parallel- group, enriched-design study of nabiximols* (Sativex((R))), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis. *Eur J Neurol* 2011;18(9):1122-31. doi: 10.1111/j.1468-1331.2010.03328.x [published Online First: 2011/03/03]
5. NCT00710424. A Study of Sativex® for Pain Relief Due to Diabetic Neuropathy: <https://ClinicalTrials.gov/show/NCT00710424>, 2006.
6. Schimrigk S, Marziniak M, Neubauer C, et al. Dronabinol Is a Safe Long-Term Treatment Option for Neuropathic Pain Patients. *European neurology* 2017;78(5-6):320-29. doi: 10.1159/000481089 [published Online First: 2017/10/27]
7. Selvarajah D, Gandhi R, Emery CJ, et al. Randomized placebo-controlled double-blind clinical trial of cannabis-based medicinal product (Sativex) in painful diabetic neuropathy: depression is a major confounding factor. *Diabetes Care* 2010;33(1):128-30. doi: 10.2337/dc09-1029 [published Online First: 2009/10/08]

eTable 6. ICEMAN criteria for assessing the credibility of subgroup effects

| Criteria | Subgroup effects of neuropathic vs non-neuropathic pain for outcomes below | | |
|---|--|---|--|
| | Pain | Social function | Discontinuation due to adverse events (non-enriched) |
| 1: Is the analysis of effect modification based on comparison within rather than between trials? | Between-study | Between-study | Between-study |
| 2: For within-trial comparisons, is the effect modification similar from trial to trial? | Not applicable | Not applicable | Not applicable |
| 3: For between-trial comparisons, is the number of trials large? | Large (55 studies with non-neuropathic pain; 26 studies with neuropathic pain) | Large (11 studies with non-neuropathic pain; 8 study with neuropathic pain) | Large (33 studies with non-neuropathic pain; 17 studies with neuropathic pain) |
| 4: Was the direction of effect modification correctly hypothesized a priori? | Probably no (opposite) | Probably no (opposite) | Probably no (opposite) |
| 5: Does a test for interaction suggest that chance is an unlikely explanation of the apparent effect modification? | Chance an unlikely explanation ($p=0.004$) | Chance a likely explanation ($p=0.047$) | Chance a very likely explanation ($p=0.052$) |
| 6: Did the authors test only a small number of effect modifiers or consider the number in their statistical analysis? | Probably no (5 factors) | Probably no (5 factors) | Probably no (5 factors) |
| 7: Did the authors use a random effects model? | Definitely yes | Definitely yes | Definitely yes |
| 8: If the effect modifier is a continuous variable, were arbitrary cut points avoided? | NA | NA | NA |
| 9 Optional: Are there any additional considerations that may increase or decrease credibility? | | | |
| The effect modification persisted after adjustment for other potential effect modifiers | NA | NA | NA |
| The effect modification is consistent across related outcomes | Yes | Yes | Yes |
| A sensitivity analysis suggested robustness to relevant assumptions | NA | NA | NA |
| Effect modification supported by external evidence | NA | NA | NA |
| “Dose-response effect” across levels of the effect modifier | NA | NA | NA |
| Risk of bias of the main effects of the individual RCTs or the meta-analysis | NA | NA | NA |
| The meta-analysis had had exceptionally high power to detect the effect modification | NA | NA | NA |
| Overall credibility | Low | Very low | Very low |

eTable 7. Subgroup analysis for pain and secondary outcomes with moderate to high certainty evidence

| Subgroup factors | | Pain relief | | | Physical functioning | | | Role functioning | | | Social functioning | | | Discontinuations due to adverse events (non-enriched) | | | |
|------------------------|-----------------|-------------|-----------------------|---------|----------------------|-------------------------|---------|------------------|--------------------------|---------|--------------------|--------------------------|---------|---|------------------------|---------|--|
| | | No studies | WMD 95% CrI | p-value | No studies | WMD 95% CrI | p-value | No studies | WMD 95% CrI | p-value | No studies | WMD 95% CrI | p-value | No studies | OR 95% CrI | p-value | |
| Clinical condition | Neuropathic | 26 | 0.74 (0.30,1.12) | 0.004 | 11 | -0.67 (-4.46, 3.28) | 0.55 | 8 | -4.66 (-21.16,5.49) | 0.10 | 8 | -8.09 (-16.89,-0.69) | 0.047 | 17 | 0.91 (0.48, 1.76) | 0.052 | |
| | Non-neuropathic | 55 | -0.12 (-0.55,0.30) | | 32 | 0.97 (-2.67, 4.72) | | 9 | 9.81 (-1.55,21.10) | | 11 | 1.01 (-3.01,4.75) | | 33 | *0.34* (0.15, 0.67) | | |
| Length of follow-u | ≤ 2 months | 39 | 0.04 (-0.36,0.45) | 0.228 | 17 | 2.35 (-2.72,6.56) | 0.59 | 10 | 8.59 (-3.64,20.37) | 0.14 | 10 | -0.31 (-8.27,7.79) | 0.70 | 29 | *0.42* (0.20, 0.79) | 0.338 | |
| | >2 months | 43 | 0.41 (-0.04,0.85) | | 27 | -0.75 (-3.83, 2.38) | | 8 | -2.48 (-11.89, 5.23) | | 10 | -2.26 (-9.50,2.29) | | 22 | 0.65 (0.37, 1.16) | | |
| Adequate randomization | Yes | 49 | 0.14 (-0.25,0.53) | 0.506 | 31 | 0.36 (-2.14, 3.03) | 0.95 | 11 | 2.92 (-9.96,15.78) | 0.55 | 15 | 0.07 (-4.45,4.34) | 0.35 | 36 | *0.48* (0.27, 0.79) | 0.375 | |
| | No | 33 | 0.37 (-0.19,0.92) | | 13 | 0.01 (-10.42, 9.03) | | 7 | -4.55 (-26.29,14.71) | | 5 | -6.93 (-21.75,6.27) | | 15 | 0.77 (0.31, 1.86) | | |
| Adequate concealment | Yes | 59 | 0.25 (-0.08,0.58) | NA | 34 | 0.87 (-1.43, 3.37) | NA | 13 | -0.81 (-6.88,5.75) | NA | 16 | -2.02 (-6.75,1.60) | NA | 39 | *0.51* (0.31, 0.79) | NA | |
| | No | NA | NA | | NA | NA | | NA | NA | | NA | NA | | NA | NA | | |
| Industry funded trials | Yes | 65 | 0.23 (-0.13,0.58) | 0.877 | 35 | 0.72 (-2.02, 3.52) | 0.36 | 13 | -0.71 (-6.86,5.72) | 0.66 | 16 | -0.62 (-4.94,2.69) | 1.00 | 39 | *0.55* (0.33, 0.92) | 0.484 | |
| | No | 10 | 0.32 (-0.78,1.39) | | 6 | -4.57 (-15.20, 6.66) | | 5 | -4.59 (-18.01,14.04) | | 4 | -0.62 (-10.78,10.11) | | 6 | 0.77 (0.09, 3.75) | | |
| Loss to follow-up | High (≥20%) | 60 | *0.53* (0.08,0.98) | 0.074 | 34 | -0.39 (-5.45, 4.52) | 0.51 | 14 | 1.40 (-3.77, 8.21) | 0.21 | 15 | -3.31 (-8.10,1.48) | 0.66 | 37 | 0.63 (0.36, 1.11) | 0.790 | |
| | Low (<20%) | 22 | -0.09 (-0.64,0.38) | | 10 | 0.86 (-3.74, 6.97) | | 4 | -18.49 (-51.56,8.85) | | 5 | 0.32 (-17.97,13.13) | | 14 | 0.79 (0.13, 2.97) | | |
| Study design | Enrichment | 22 | -0.65 (-1.65,0.35) | 0.093 | NA | NA | NA | 3 | -22.92 (-61.99,16.11) | 0.24 | 3 | -14.19 (-40.56,12.39) | 0.36 | NA | | | |
| | Non-enrichment | 60 | 0.25 (-0.07,0.57) | | 34 | 0.37 (-2.57, 3.19) | | 15 | 0.55 (-5.34, 7.41) | | 17 | -1.54 (-6.21,2.32) | | | | | |

All values in bold are statistically significant at the 0.05 significance level. * = unless otherwise indicated. Results are cannabis for medical use versus opioids. p-value based on test of interaction

Table 8. Subgroup analysis for secondary outcomes with low certainty evidence

| Subgroup factors | | Emotional functioning | | | | Sleep quality | | | | Discontinuations due to AEs (enriched studies) | | | |
|------------------------|-----------------|-----------------------|-------|-----------------|---------|---------------|-------|-----------------|---------|---|------|---------------|---------|
| | | No studies | WMD | 95% CrI | p-value | No studies | WMD | 95% CrI | p-value | No studies | OR | 95% CrI | p-value |
| Clinical condition | Neuropathic | 10 | 0.15 | (−4.07, 4.56) | 0.783 | 10 | −3.44 | (−12.56, 6.03) | 0.323 | 4 | NA | NA | NA |
| | Non-neuropathic | 19 | 0.91 | (−2.47, 4.08) | | 21 | 2.68 | (−5.25, 10.38) | | 18 | NA | NA | |
| Length of follow-up | ≤ 2 months | 13 | 0.80 | (−4.77, 5.19) | 0.965 | 16 | −0.28 | (−7.45, 7.26) | 0.848 | 4 | | | NA |
| | >2 months | 17 | 0.93 | (−2.11, 4.08) | | 16 | 0.75 | (−6.96, 8.09) | | 18 | | | |
| Adequate randomization | Yes | 18 | 2.55 | (−0.74, 5.64) | 0.119 | 21 | 0.04 | (−6.62, 6.70) | 0.638 | 11 | NA | NA | NA |
| | No | 12 | −1.14 | (−4.54, 2.20) | | 11 | 3.21 | (−8.92, 13.92) | | 11 | 2.05 | (0.09, 93.28) | |
| Adequate concealment | Yes | 22 | 1.44 | (−0.91, 3.62) | NA | 25 | 0.20 | (−6.32, 6.44) | NA | 15 | 0.91 | (0.08, 10.88) | NA |
| | No | NA | NA | NA | | NA | NA | NA | | NA | NA | NA | |
| Industry funded trials | Yes | 24 | 2.27 | (−1.19, 5.68) | 0.363 | 29 | 0.71 | (−4.94, 6.20) | 0.684 | 21 | 0.79 | (0.07, 8.97) | NA |
| | No | 5 | −1.71 | (−9.86, 5.86) | | 3 | −3.12 | (−20.25, 14.88) | | NA | NA | NA | |
| Loss to follow-up | High (≥20%) | 25 | 0.38 | (−2.41, 3.04) | 0.997 | 20 | 0.86 | (−9.30, 10.66) | 0.958 | NA | NA | NA | NA |
| | Low (<20%) | 5 | 0.36 | (−8.02, 9.38) | | 12 | 1.13 | (−11.54, 12.53) | | 5 | 0.65 | (0.04, 10.18) | |
| Study design | Enrichment | 7 | 4.05 | (−10.97, 19.04) | 0.695 | 6 | 7.27 | (−4.35, 17.38) | 0.184 | − | − | − | − |
| | Non-enrichment | 23 | 1.02 | (−1.32, 3.12) | | 26 | −1.21 | (−7.49, 4.96) | | − | − | − | |

Results are cannabis for medical use versus opioids. Inadequate concealment not applicable because all cannabis for medical use trials had adequate concealment.

p-value based on test of interaction

eTable 9. Network meta-regression for pain outcome, length of follow-up and sample size

| Pain relief, network estimate WMD (95% CrI) | | | |
|---|------------------|--------------------------------------|-------------------------------------|
| Covariate, length of follow-up | Placebo | Cannabis for medical use | Opioids |
| Unadjusted model | | | |
| Placebo | | -0.60 (-0.87, -0.33) | -0.83 (-0.97, -0.70) |
| | | -1.39 ¹ (-2.04, -0.76) | -0.23 (-0.53, 0.06) |
| | | -1.21 ² (-1.53, -0.91) | 0.18 ³ (-0.55, 0.89) |
| Covariate, sample size | Unadjusted model | | |
| Placebo | | -0.60 (-0.87, -0.33) | -0.83 (-0.97, -0.70) |
| | | -0.91 ¹ (-1.37, -0.46) | -0.23 (-0.53, 0.06) |
| | | -0.97 ² (-1.15, -0.78) | -0.06 ³ (-0.54, 0.44) |

All values in bold are statistically significant at the 0.05 significance level.

¹ MD for cannabis for medical use versus placebo; ² MD for Opioids versus placebo; ³ MD for Opioids versus cannabis for medical use. DIC value between adjusted and unadjusted models is less than 5

eTable 10. Network meta-regression for secondary outcomes, length of follow-up and sample size

| Physical functioning, network estimate WMD (95% CrI) | | | |
|--|------------------|------------------------------------|--------------------------------------|
| Covariate, length of follow-up | Placebo | Cannabis for medical use | Opioids |
| Unadjusted model | | | |
| Placebo | | 2.52 (0.37, 4.91) | 2.05 (1.00, 3.29) |
| | | 7.23 ¹ (2.10, 12.77) | -0.47 (-2.99, 1.97) |
| | | 3.00 ² (0.43, 5.84) | -4.20 ³ (-10.32, 1.54) |
| Covariate, sample size | Unadjusted model | | |
| Placebo | | 2.52 (0.37, 4.91) | 2.05 (1.00, 3.29) |
| | | 4.19 ¹ (0.94, 7.57) | -0.47 (-2.99, 1.97) |
| | | 2.75 ² (1.16, 4.65) | -1.44 (-5.08, 2.33) |

All values in bold are statistically significant at the 0.05 significance level.

¹ MD for cannabis for medical use versus placebo; ² MD for Opioids versus placebo; ³ MD for Opioids versus cannabis for medical use. DIC value between adjusted and unadjusted models is less than 5

| Emotional functioning, network estimate WMD (95% CrI) | | | |
|--|------------------------------------|-------------------------------------|------------------------|
| Covariate, length of follow-up | Placebo | Cannabis for medical use | Opioids |
| Unadjusted model | | | |
| Placebo | | 0.70 (-1.42, 2.84) | -0.15 (-1.10, 0.92) |
| | 0.96 ¹ (-4.81, 6.57) | | -0.85 (-3.18, 1.55) |
| | 0.32 ² (-2.68, 3.59) | -0.67 ³ (-6.78, 5.92) | |
| Covariate, sample size | Unadjusted model | | |
| Placebo | | 0.70 (-1.42, 2.84) | -0.15 (-1.10, 0.92) |
| | 1.11 ¹ (-2.04, 4.24) | | -0.85 (-3.18, 1.55) |
| | 0.59 ² (-0.99, 2.31) | -0.50 ³ (-3.98, 3.06) | |

¹ MD for cannabis for medical use versus placebo; ² MD for Opioids versus placebo; ³ MD for Opioids versus cannabis for medical use. DIC value between adjusted and unadjusted models is less than 5

| Role functioning, network estimate WMD (95% CrI) | | | |
|---|--------------------------------------|---------------------------------------|-----------------------|
| Covariate, length of follow-up | Placebo | Cannabis for medical use | Opioids |
| Unadjusted model | | | |
| Placebo | | 0.88 (-3.78, 6.05) | 0.94 (-1.26, 3.17) |
| | 14.41 ¹ (-0.89, 31.01) | | 0.05 (-5.60, 5.16) |
| | 2.22 ² (-2.95, 8.49) | -12.11 ³ (-29.35, 4.07) | |
| Covariate, sample size | Unadjusted model | | |
| Placebo | | 0.88 (-3.78, 6.05) | 0.94 (-1.26, 3.17) |
| | 5.40 ¹ (-5.80, 16.94) | | 0.05 (-5.60, 5.16) |
| | 2.25 ² (-0.87, 5.72) | -3.13 ³ (-14.98, 8.65) | |

¹ MD for cannabis for medical use versus placebo; ² MD for Opioids versus placebo; ³ MD for Opioids versus cannabis for medical use. DIC value between adjusted and unadjusted models is less than 5

| Social functioning, network estimate WMD (95% CrI) | | | |
|---|-------------------------------------|---------------------------------------|------------------------|
| Covariate, length of follow-up | Placebo | Cannabis for medical use | Opioids |
| Unadjusted model | | | |
| Placebo | | 1.70 (-3.28, 8.13) | 1.17 (-1.72, 4.58) |
| | 2.43 ¹ (-7.21, 12.74) | | -0.55 (-7.41, 5.34) |
| | 1.98 ² (-3.14, 6.89) | -0.37 ³ (-11.76, 10.10) | |
| Covariate, sample size | Unadjusted model | | |
| Placebo | | 1.70 (-3.28, 8.13) | 1.17 (-1.72, 4.58) |
| | 0.16 ¹ (-7.66, 8.04) | | -0.55 (-7.41, 5.34) |
| | 1.61 ² (-1.10, 4.27) | 1.45 ³ (-6.89, 9.64) | |

¹ MD for cannabis for medical use versus placebo; ² MD for Opioids versus placebo; ³ MD for Opioids versus cannabis for medical use. DIC value between adjusted and unadjusted models is less than 5

| Sleep quality, network estimate WMD (95% CrI) | | | |
|--|--|--------------------------------------|-----------------------------|
| Covariate, length of follow-up | Placebo | Cannabis for medical use | Opioids |
| Unadjusted model | | | |
| Placebo | | 5.95 (1.82, 10.24) | 5.46 (2.62, 8.59) |
| Cannabis for medical use | 8.74 ¹ (-1.97, 19.32) | | -0.49 (-5.59, 4.72) |
| Opioids | 9.10² (1.91, 16.26) | 0.28 ³ (-12.32, 13.04) | |
| Unadjusted model | | | |
| Placebo | | 5.95 (1.82, 10.24) | 5.46 (2.62, 8.59) |
| Cannabis for medical use | 7.40 ¹ (0.75, 14.02) | | -0.49 (-5.59, 4.72) |
| Opioids | 8.56 ² (4.41, 12.75) | 1.16 ³ (-6.58, 9.00) | |

All values in bold are statistically significant at the 0.05 significance level.

¹ MD for cannabis for medical use versus placebo; ² MD for Opioids versus placebo; ³ MD for Opioids versus cannabis for medical use. DIC value between adjusted and unadjusted models is less than 5

Discontinuations due to adverse events (enriched trials)

Results are not reliable due to small number of studies. Number of studies for cannabis for medical use versus placebo = 2.

| Discontinuations due to adverse events (non-enriched trials), network estimate OR (95% CrI) | | | |
|--|---|---|-----------------------------|
| Covariate, length of follow-up | Placebo | Cannabis for medical use | Opioids |
| Unadjusted model | | | |
| Placebo | | 1.80 (1.19, 2.63) | 3.27 (2.71, 3.90) |
| Cannabis for medical use | 0.75 ¹ (0.27, 1.84) | | 1.81 (1.21, 2.81) |
| Opioids | 2.05² (1.40, 2.95) | 2.70³ (1.08, 8.13) | |
| Unadjusted model | | | |
| Placebo | | 1.80 (1.19, 2.63) | 3.27 (2.71, 3.90) |
| Cannabis for medical use | 0.79 ¹ (0.32, 1.83) | | 1.81 (1.21, 2.81) |
| Opioids | 2.87² (2.15, 3.79) | 3.65³ (1.54, 9.22) | |

All values in bold are statistically significant at the 0.05 significance level.

¹ MD for cannabis for medical use versus placebo; ² MD for Opioids versus placebo; ³ MD for Opioids versus cannabis for medical use.

eTable 11. Network meta-analysis results for pain outcome by MME thresholds

| Placebo | Cannabis for medical use | Opioid MME > 100 mg | Opioid MME < 50mg | Opioid MME 50 - 99mg |
|-------------------------|--------------------------|-----------------------|-----------------------|----------------------|
| -0.61 (-0.90, -0.32) | -0.31 (-0.73, 0.11) | | | |
| -0.92 (-1.23, -0.62) | | 0.11 (-0.27, 0.49) | | |
| -0.81 (-1.04, -0.58) | -0.20 (-0.56, 0.17) | | 0.00 (-0.34, 0.34) | |
| -0.81 (-1.06, -0.55) | -0.20 (-0.58, 0.19) | 0.11 (-0.28, 0.51) | | Opioid MME 50 - 99mg |

All values in bold are statistically significant at the 0.05 significance level

eTable 12. Network meta-analysis results for secondary outcomes by MME thresholds

| Physical functioning | | | | |
|-----------------------------|--------------------------|-----------------------|-----------------------|----------------------|
| Placebo | Cannabis for medical use | Opioid MME > 100 mg | Opioid MME < 50mg | Opioid MME 50 - 99mg |
| 2.30 (0.35, 4.66) | -1.14 (-4.61, 1.88) | | | |
| 1.14 (-1.28, 3.63) | -0.04 (-2.65, 2.59) | 1.10 (-1.66, 4.36) | | |
| 2.25 (0.75, 4.26) | 0.88 (-1.96, 3.56) | 2.02 (-0.91, 5.28) | 0.93 (-1.64, 3.29) | Opioid MME 50 - 99mg |
| 3.17 (1.47, 5.23) | | | | |

All values in bold are statistically significant at the 0.05 significance level

Emotional functioning

| Placebo | Cannabis for medical use | Opioid MME > 100 mg | Opioid MME < 50mg | Opioid MME 50 - 99mg |
|------------------------|--------------------------|------------------------|------------------------|----------------------|
| 0.66 (-1.01, 2.36) | -1.76 (-3.89, 0.44) | | | |
| -1.11 (-2.40, 0.34) | -0.59 (-2.75, 1.52) | 1.17 (-0.83, 3.03) | | |
| 0.07 (-1.28, 1.42) | -1.93 (-3.87, 0.40) | -0.19 (-1.83, 1.96) | -1.36 (-2.96, 0.87) | Opioid MME 50 - 99mg |
| -1.29 (-2.35, 0.37) | | | | |

Role functioning

| Placebo | Cannabis for medical use | Opioid MME > 100 mg | Opioid MME < 50mg | Opioid MME 50 - 99mg |
|------------------------|--------------------------|------------------------|------------------------|----------------------|
| 1.08 (-4.16, 6.90) | -3.77 (-12.25, 3.97) | | | |
| -2.70 (-8.69, 3.17) | 1.72 (-5.28, 9.30) | 5.47 (-1.54, 13.89) | | |
| 2.77 (-1.51, 8.36) | -0.61 (-8.18, 6.47) | 3.19 (-4.34, 10.91) | -2.28 (-9.85, 3.98) | Opioid MME 50 - 99mg |
| 0.48 (-4.29, 5.37) | | | | |

Social functioning

| Placebo | Cannabis for medical use | Opioid MME > 100 mg | Opioid MME < 50mg | Opioid MME 50 - 99mg |
|------------------------|---------------------------------|-------------------------------|-----------------------------|-----------------------------|
| -1.33 (-5.06, 1.68) | -0.58 (-5.42, 4.77) | 1.57 (-4.33, 7.76) | 2.30 (-3.22, 8.34) | |
| -1.91 (-5.87, 1.82) | 1.00 (-4.44, 7.11) | 3.84 (-0.81, 9.61) | | |
| -0.35 (-4.96, 4.41) | | | | |
| 1.93 (-1.13, 5.82) | 3.26 (-0.97, 8.96) | | | |

Sleep quality

| Placebo | Cannabis for medical use | Opioid MME > 100 mg | Opioid MME < 50mg | Opioid MME 50 - 99mg |
|-------------------------------|---------------------------------|-------------------------------|-----------------------------|-----------------------------|
| 5.93 (1.82, 10.24) | | | | |
| 0.09 (-11.56, 11.64) | -5.86 (-18.31, 6.37) | 4.29 (-7.92, 17.09) | | |
| 4.39 (-0.12, 9.36) | -1.54 (-7.72, 4.88) | | | |
| 9.56 (4.73, 14.56) | 3.62 (-2.87, 10.08) | 9.47 (-3.02, 22.16) | 5.17 (-1.77, 11.81) | |

All values in bold are statistically significant at the 0.05 significance level

Discontinuations due to adverse events (enriched trials)

| Placebo | Cannabis for medical use | Opioid MME > 100 mg | Opioid MME < 50mg | Opioid MME 50 - 99mg |
|-----------------------|---------------------------------|-------------------------------|-----------------------------|-----------------------------|
| 0.99 (0.10, 10.65) | | | | |
| 1.23 (0.71, 2.18) | 1.25 (0.11, 13.76) | 0.87 (0.40, 1.84) | | |
| 1.07 (0.63, 1.80) | 1.07 (0.10, 11.38) | | | |
| 1.52 (0.80, 2.72) | 1.52 (0.13, 16.32) | 1.23 (0.53, 2.73) | 1.42 (0.63, 3.12) | |

Discontinuations due to adverse events (non-enriched trials)

| Placebo | Cannabis for medical use | Opioid MME > 100 mg | Opioid MME < 50mg | Opioid MME 50 - 99mg |
|------------------------------|---------------------------------|-------------------------------|-----------------------------|-----------------------------|
| 1.83 (1.19, 2.67) | | | | |
| 3.45 (2.12, 5.28) | 1.88 (1.06, 3.44) | 0.85 (0.52, 1.51) | | |
| 2.92 (2.28, 3.88) | 1.60 (1.01, 2.74) | | | |
| 4.02 (2.86, 5.31) | 2.19 (1.36, 3.57) | 1.17 (0.68, 1.98) | 1.38 (0.86, 1.99) | |

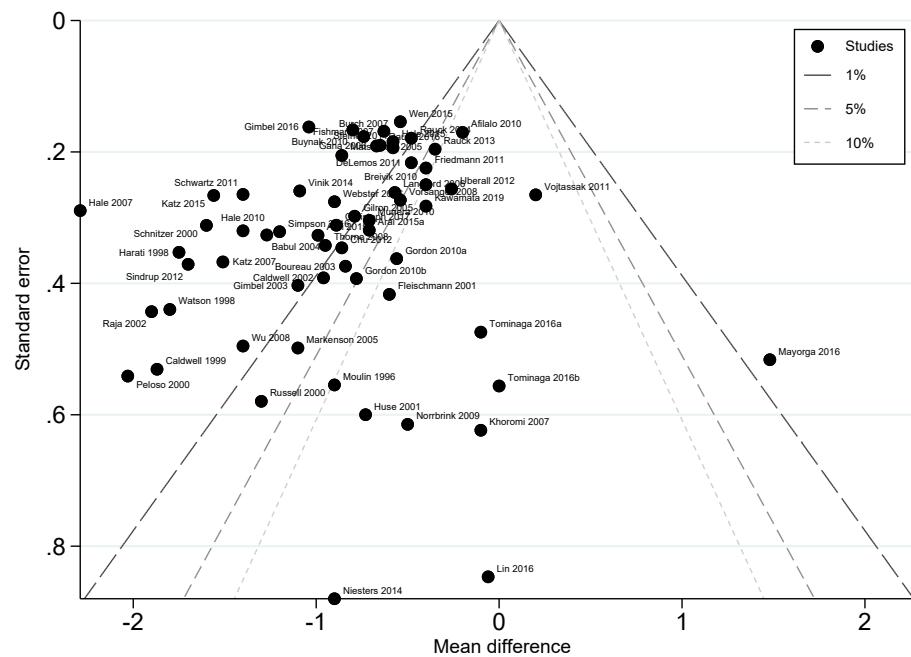
All values in bold are statistically significant at the 0.05 significance level

Table 13. Pain studies from JAMA 2018 systematic review & meta-analysis included & excluded in network meta-analysis

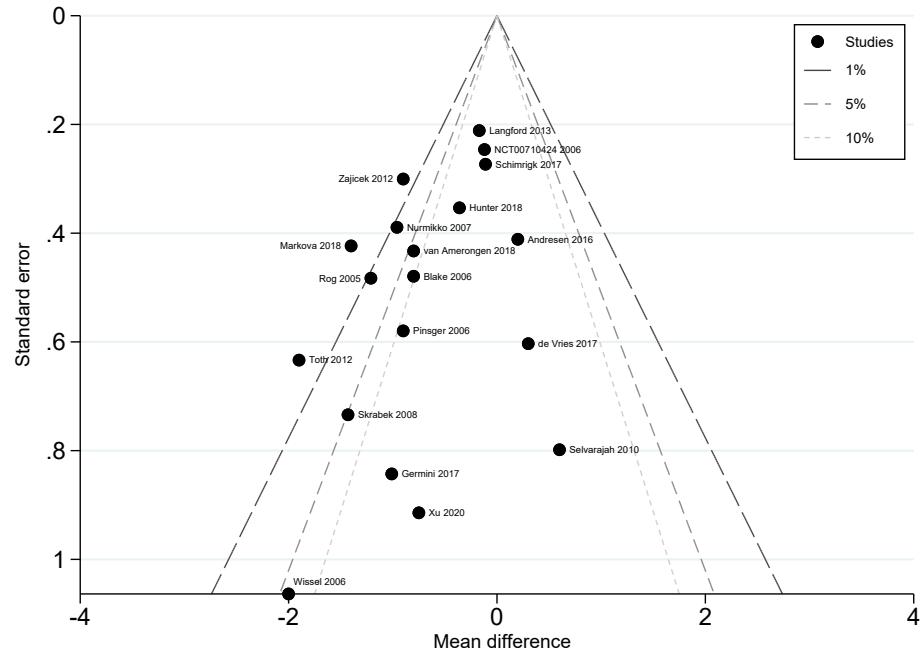
| Author | Year | Inclusion or Exclusion reason | Author | Year | Inclusion or Exclusion reason |
|---|------|-------------------------------|-------------|------|-------------------------------|
| Fleischmann | 2001 | Included | Schwartz | 2011 | Included |
| Bennett | 2003 | Combination products | Steiner | 2011 | Included |
| Ruoff | 2003 | Combination products | Vojtassak | 2011 | Included |
| Babul | 2004 | Included | Rauck | 2013 | Included |
| Emkey | 2004 | Combination products | Rauck | 2014 | Included |
| Peloso | 2004 | Combination products | Vinik | 2014 | Included |
| Gana | 2006 | Included | Arai | 2015 | Included |
| Webster | 2006 | Included | Arai | 2015 | Included |
| Burch | 2007 | Included | Hale | 2015 | Included |
| Fishman | 2007 | Included | Katz | 2015 | Included |
| Hale | 2007 | Included | Rauck | 2015 | Combination products |
| Katz | 2007 | Included | Trenkwalder | 2015 | Combination products |
| Hanna | 2008 | Combination products | Wen | 2015 | Included |
| Vorsanger | 2008 | Included | Gimbel | 2016 | Included |
| Afilalo | 2010 | Included | Mayorga | 2016 | Included |
| Breivik | 2010 | Included | Rauck | 2016 | Included |
| Buynak | 2010 | Included | Simpson | 2016 | Included |
| Hale | 2010 | Included | Tominaga | 2016 | Included |
| Katz | 2010 | Combination products | Tominaga | 2016 | Included |
| DeLemos | 2011 | Included | Christoph | 2017 | Included |
| Friedmann | 2011 | Included | Serrie | 2017 | Incomplete reporting |
| Total number of studies 42; 9 exclusions; 33 inclusions | | | | | |

Table 14. Pain studies included in network meta-analysis excluded from pain JAMA 2018 systematic review & meta-analysis

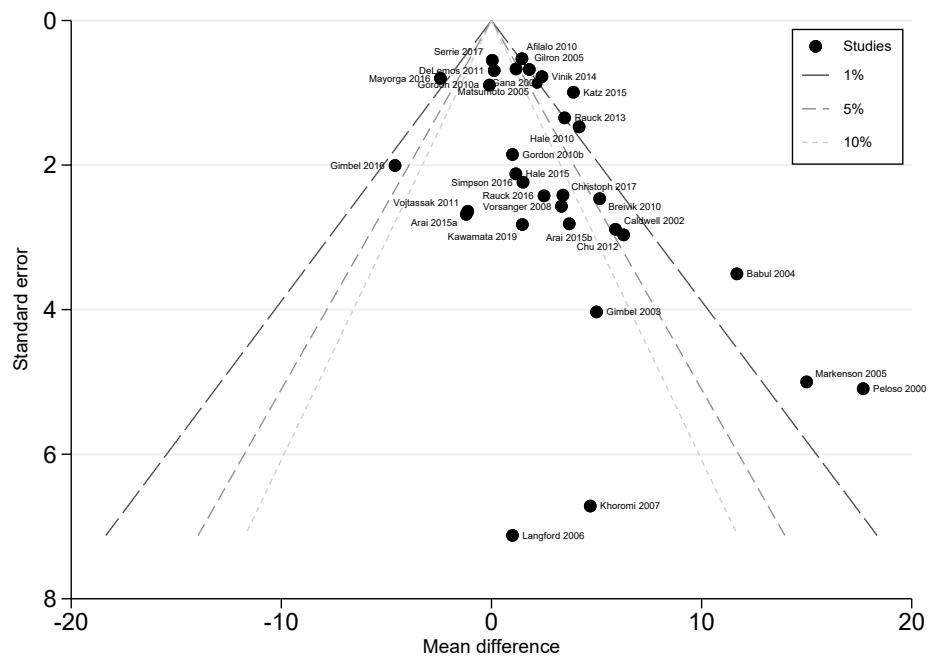
| Author | Year | Exclusion reason from JAMA review | Author | Year | Exclusion reason from JAMA review |
|-----------------------------|------|-----------------------------------|-----------|------|---|
| Moulin | 1996 | < 3months follow-up | Langford | 2006 | < 3months follow-up |
| Harati | 1998 | < 3months follow-up | Khoromi | 2007 | < 3months follow-up |
| Watson | 1998 | < 3months follow-up | Thorne | 2008 | < 3months follow-up |
| Caldwell | 1999 | < 3months follow-up | Wu | 2008 | Did not pass screening |
| Peloso | 2000 | < 3months follow-up | Norrbrink | 2009 | < 3months follow-up |
| Russell | 2000 | < 3months follow-up | Gordon | 2010 | < 3months follow-up |
| Schnitzer | 2000 | < 3months follow-up | Gordon | 2010 | < 3months follow-up |
| Huse | 2001 | < 3months follow-up | Munera | 2010 | < 3months follow-up |
| Caldwell | 2002 | < 3months follow-up | Chu | 2012 | < 3months follow-up |
| Raja | 2002 | < 3months follow-up | Sindrup | 2012 | < 3months follow-up |
| Boureau | 2003 | < 3months follow-up | Uberall | 2012 | < 3months follow-up |
| Gimbel | 2003 | < 3months follow-up | Niesters | 2014 | < 3months follow-up |
| Gilron | 2005 | < 3months follow-up | Lin | 2016 | < 3months follow-up |
| Markenson | 2005 | Did not pass screening | Kawamata | 2019 | Published after search execution end date |
| Matsumoto | 2005 | < 3months follow-up | | | |
| Total number of studies 29. | | | | | |

eFigure 18. Funnel plot for pain for randomized trials of opioids versus placebo

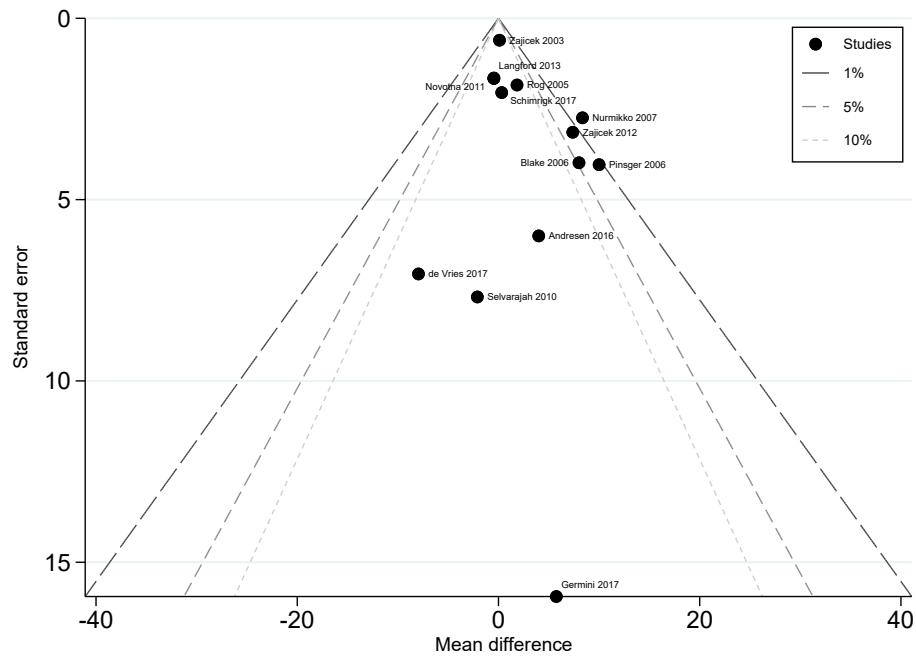
Egger's test p-value = 0.039

eFigure 19. Funnel plot for pain for randomized trials of cannabis for medical use versus placebo

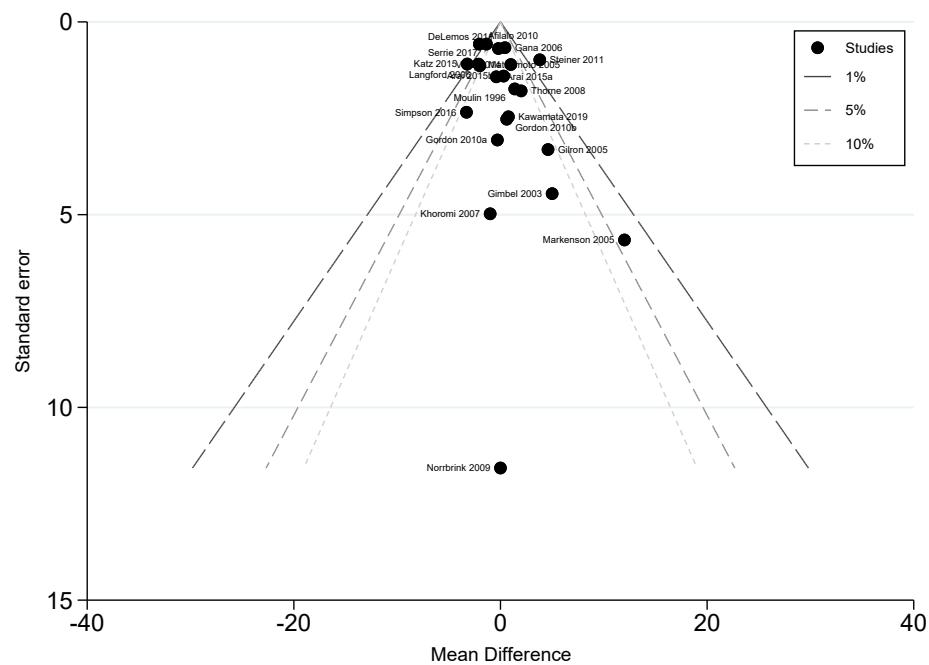
Egger's test p-value = 0.044

eFigure 20. Funnel plot for physical functioning for randomized trials of opioids versus placebo

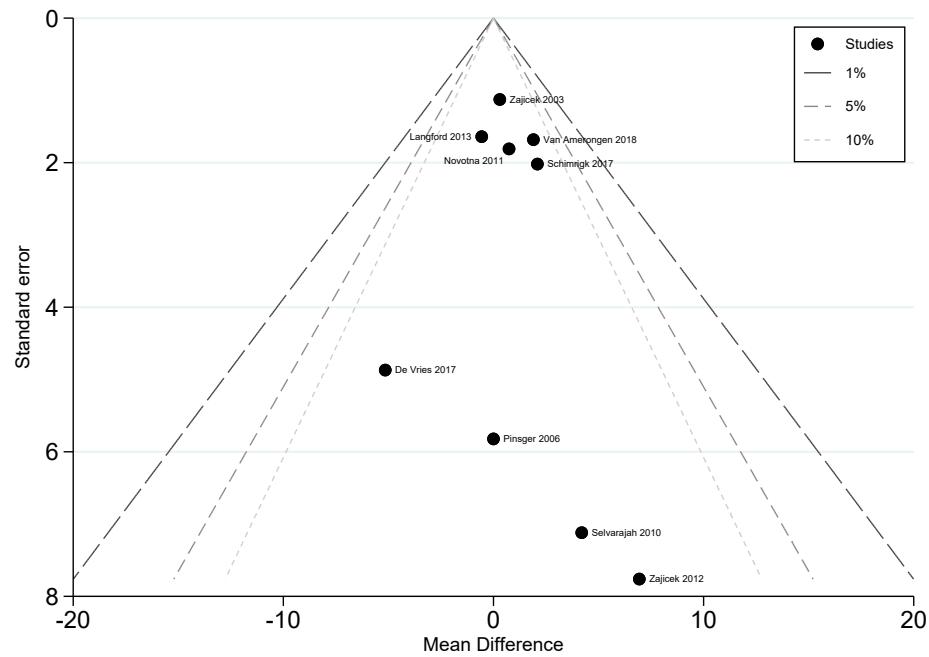
Egger's test p-value = 0.015

eFigure 21. Funnel plot for physical functioning for randomized trials of cannabis for medical use versus placebo

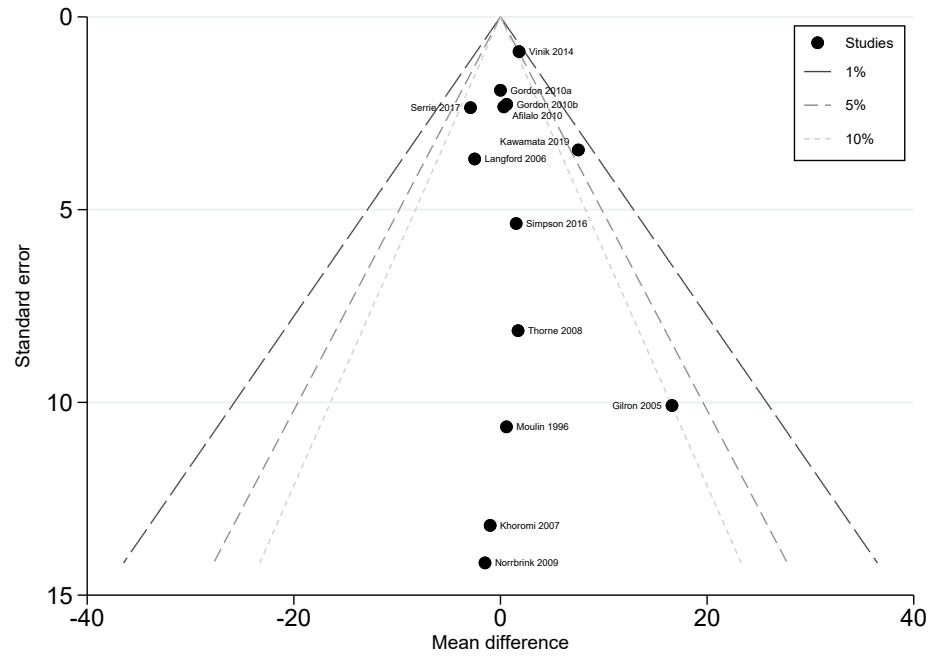
Egger's test p-value = 0.098

eFigure 22. Funnel plot for emotional functioning for randomized trials of opioids versus placebo

Egger's test p-value = 0.121

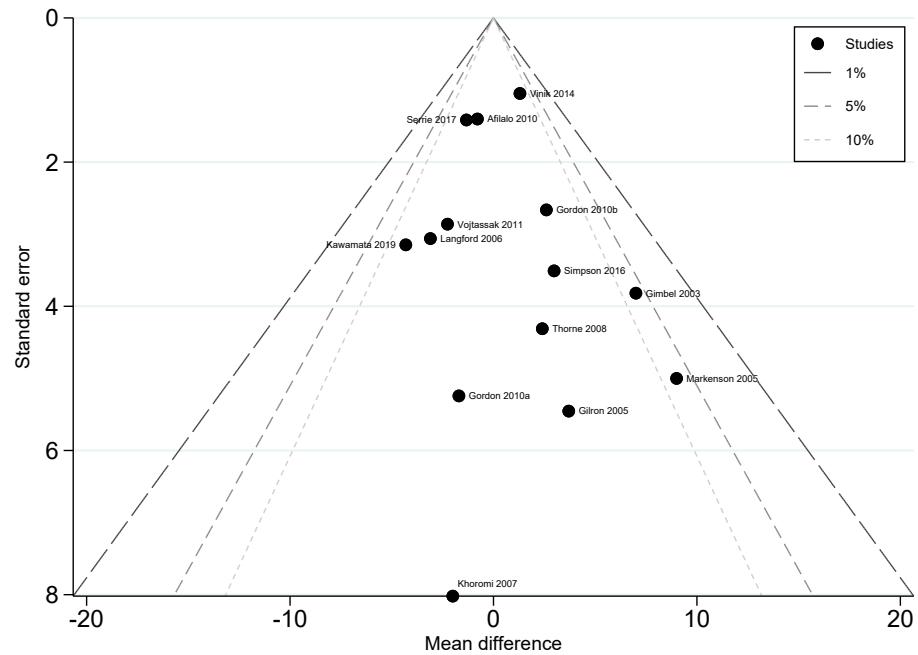
eFigure 23. Funnel plot for emotional functioning for randomized trials of cannabis for medical use versus placebo

Egger's test p-value = 0.71

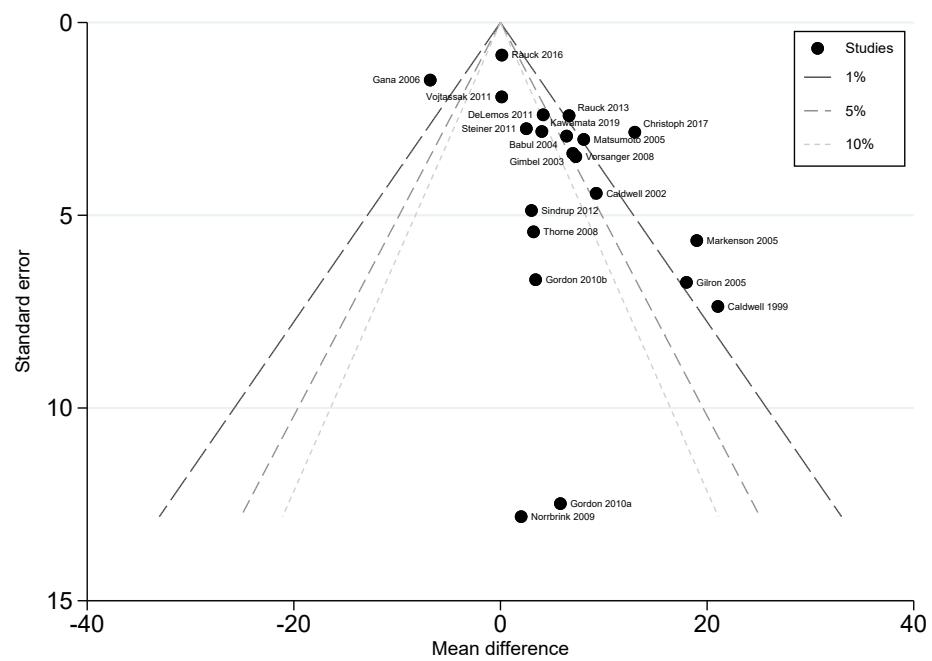
eFigure 24. Funnel plot for role functioning for randomized trials of opioids versus placebo

Egger's test p-value = 0.967

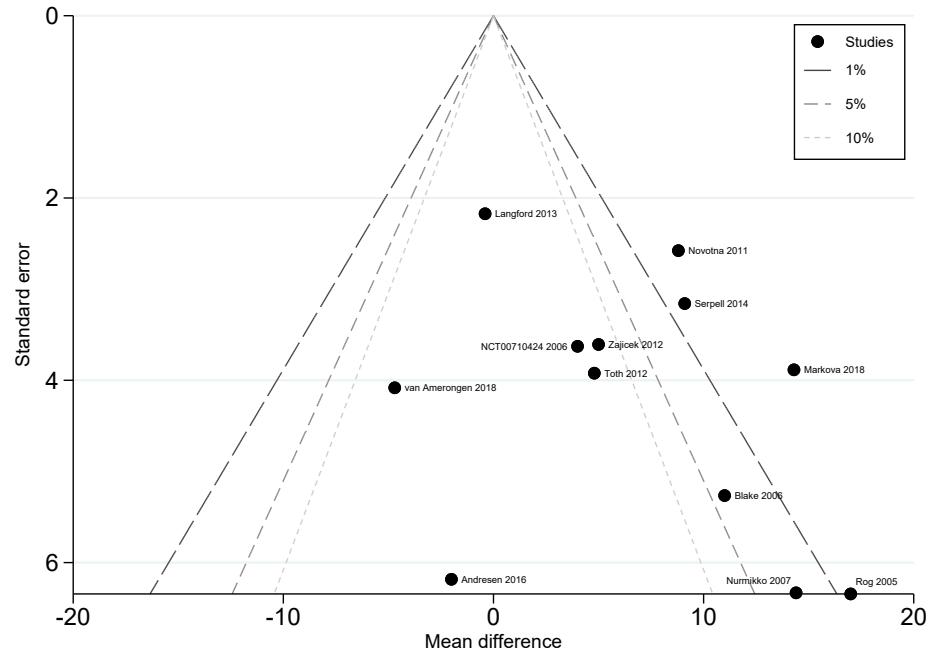
eFigure 25. Funnel plot for social functioning for randomized trials of opioids versus placebo



Egger's test p-value = 0.548

eFigure 26. Funnel plot for sleep quality for randomized trials of opioids versus placebo

Egger's test p-value = 0.003

eFigure 27. Funnel plot for sleep quality for randomized trials of cannabis for medical use versus placebo

Egger's test p-value = 0.258